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ANNALS OF
INTERNAL MEDICINE

VOLUME 10 AUGUST, 1936 NUMBER 2

THE PRESENT STATUS OF THE TREATMENT OF PULMONARY TUBERCULOSIS*

By LAWRASON BROWN, M.D., F.A.C.P., *Saranac Lake, N. Y.*

THE marked decrease in the mortality of pulmonary tuberculosis is undoubtedly due to many causes. It is not, many hold, a true measure of the decrease of the morbidity of the disease. Pulmonary tuberculosis is still a very menacing cause of death to both sexes during the period of greatest bodily and mental activity. The keen desire for a cure for tuberculosis, a true therapia magna sterilisans, so widely spread at the beginning of the century, is now less evident. Some foundations and laboratories consider tuberculosis an unpromising field of endeavor and have left it largely to the clinicians and sanitarians, who have contributed much. Few will question that more efficient treatment is one of the causes of the decreased mortality. Such treatment acts in two ways: it frees the sputum of tubercle bacilli and aids the victims to arrest really and permanently their disease or to live long enough to die of other causes.

To assess the value of different methods of treatment in any chronic disease is far from simple. The faith of him who introduces a new measure is too often passed on to him who receives it. Several years ago I spoke to some members of this College of the influence of the mental aspects upon the results of the treatment of pulmonary tuberculosis. I attempted to show at that time what a powerful effect suggestion, applied consciously or unconsciously, played in the results of treatment. I think I recalled at that time the practice attributed to an acquaintance who, poising the tuberculin containing syringe, uttered just as he inserted the needle, the incantation, "This is the life giving fluid." Any patient to whom he had in the vernacular "sold the idea" of tuberculin responded no doubt as fully as those lulled to sleep with the words, "You are better in every way every day." Misery undoubtedly begets credulity. This is probably the explanation of why many measures for the relief of pulmonary tuberculosis are helpful in the hands that introduce them, failures in the hands of others.

We hear today on all sides how the treatment of pulmonary tuberculosis has been revolutionized since the introduction of collapse therapy. For

* Presented at the Detroit meeting of the American College of Physicians, March 6, 1936.

the " far advanced " patient and for many of the progressively " moderately advanced " patients this is true. We all hail the advances made possible by the fundamental studies not only of the surgeons but also of the physicians. Brauer, a physician of Marburg, and later of Hamburg, spread the idea of collapse treatment throughout Europe and even back to America after he had received the suggestion from an American surgeon. Forlanini, the father of pneumothorax, was a physician. If we really face the facts, none of us can today think of the treatment of pulmonary tuberculosis without having always before us this collapse treatment. Some of our surgical confrères almost scout the idea that pulmonary tuberculosis is anything else than a surgical disease. They would have us hurry most patients to the operating room for fear that the disease may progress too far for surgical relief. They even lead us to believe that at some stage every patient can be greatly helped by the needle or by the scalpel. After living with pulmonary tuberculosis for some 35 or 40 years I cannot accept such a statement without some reservations.

The majority of those familiar with pulmonary tuberculosis in all its stages do not hold that patients in the minimal stage require, by and large, any form of surgical treatment. Certainly the great majority have recovered without such interference, and the last word is chosen carefully. The records at the Trudeau Sanatorium reveal only 8 per cent of these " minimal " patients dead at the end of 15 years. Such patients rarely fall into the hands of the surgeons, and many surgeons are not familiar with the excellent results obtained in such patients. Indeed some surgeons speak as if patients in this early stage presented cavitation, which is entirely wrong, for cavitation places them immediately in the second or advanced group. I might go even further and state that few, very few, of these " minimal " patients, only those with definitely advancing disease after treatment by rest, exposure to fresh air, by feeding with good food, and by treatment of symptoms as they arise, require more than these simple measures. But to treat pulmonary tuberculosis successfully does necessitate familiarity with the use of these fundamental means and how to judge of their effects.

It is then extremely important to know the proper treatment of this early stage of pulmonary tuberculosis. As soon as it has been diagnosed and as soon as it is determined that the lesion is active, rigorous treatment should be instituted. Now this treatment, less empirical than it was some 35 years ago, still revolves about the triad of rest, food, and air. Experience accumulated as the years have rolled on, based upon the unfortunate outcome of the treatment of certain patients, has emphasized the fact that the knowledge of the proper use of these seemingly simple measures is not acquired in a single interview to such a degree as to lead to certain and ultimate recovery. To this end we must add to the triad the education of the patient. The fundamentals then of all successful therapy of early pulmonary tuberculosis consist of (1) rest in the beginning and properly regulated

exercise later; (2) good food; (3) fresh air; (4) and finally, to insure the permanency of the recovery, proper education of the patient.

(1) Concerning rest. Injury ever demands rest for repair. Surely the reason for pain in the universe is not only to teach the uselessness of breaking the laws of nature but also to emphasize the value of rest. Unfortunately pulmonary tuberculosis is only infrequently associated with pain and the ignorant have their fears quickly lulled into a false sense of security and of approaching well being. Weakness, they argue, can be overcome by exercise. Many, conscientiously and literally, have walked themselves into their graves. For these reasons I invariably put all such "minimal" patients to bed for a period of at least six weeks. I permit them to go to the bathroom and even certain of them to go to the table but never allow them to dress or to go up or down stairs. I attempt to explain to them why the lung requires rest for recovery. Later I get them out of bed very gradually, permitting them to begin exercise at the end of six weeks by walking one or two minutes twice a day, without dressing, and increasing the amount of walking by one or two minutes a day until they are walking 20 minutes twice a day. Then if they have a flight of steps to navigate I start them on one step a day until they reach the bottom. Not until then do they dress. Following this they walk on the street at first for 10 minutes twice a day for a week, then for 20 minutes, for 30 minutes, for three-quarters of an hour and finally for an hour twice a day. When they reach this stage they can seldom hurt themselves by walking on the level to which I have so far confined them. The recollection of this slow progress has a very salutary effect upon their future actions. My suggestion is that in proportion as you can give any organ functional rest so you can aid it to recover from tuberculosis.

(2) Concerning food. There has been abroad in the tuberculosis land an impression that if a little food was beneficial, an increase might be more quickly helpful. This was no doubt the basis for the old saying at the Trudeau Sanatorium that a patient must eat once for himself, once for the germs, and once to gain weight. You will recall that in the time of Laennec and Louis a reproach, thrown in the faces of those who advocated the early diagnosis of phthisis, was that such a diagnosis led but more surely to the grave. This rebuke, uttered both in Europe and in America, had much truth in it. About a decade later you will remember the London *Lancet* intimated that if Dr. George Bodington continued to feed his patients such food as beefsteak he would lay himself open to prosecution for malpractice. Now at this time early diagnosis of pulmonary tuberculosis was rarely made, and when made, could usually be confirmed from across the way. Such emaciation demanded food in far larger quantities than is needed for the class of patients we are now discussing. The amount of good food that has been wasted upon the early patients has been appalling and unfortunately upsetting. The strict Gerson diet, so effective in some cases of cutaneous tuberculosis (especially lupus), is far less, if at all, helpful in pulmonary

tuberculosis. For some years, in the hope of changing an exudative into a proliferative reaction, I have been using, with some encouragement, a diet high in vitamins C and D, restricting the intake of sodium chloride and giving dicalcium phosphate. I would like to suggest that the least amount of food that any patient who is under weight can gain upon is the optimum diet for that patient.

(3) Concerning fresh air. Inflammation of the lungs, it was held years ago, demanded protection: Pulmonary tuberculosis was associated with such inflammation and so required protection also. Night air was bad. Change in temperature was deleterious. So the patient should never go out at night and the temperature of the house must be kept high and not vary. Such views were as wrong as those of the *Lancet* on diet. They were based on two erroneous principles: first, that patients with pulmonary tuberculosis needed warm and equable climates, and second, that the only organ concerned in recovery was the lungs. Today we know that fresh air affects the lungs no more, no less, than it does the knee. The chief effect of aerotherapy is manifested through the skin, and a variation of 20 degrees during the 24 hours is highly desirable. These early patients should have a room connected with a porch upon which the bed can be rolled. If this cannot be had, there should be a bed on the porch and one in the room. I am no advocate of sleeping out of doors for patients who spend hours in the open air every day. During the cool and colder months I insist that the patient spend at least six or seven hours in the open, tempering the time to the vigor of the patient. Such patients can recover in a room but the psychological stimulation, apart from any other factor, makes some hours on a porch most desirable. I would suggest that recovery from pulmonary tuberculosis depends upon six or seven hours in the open, and on good ventilation during the remainder of the twenty-four.

(4) Concerning education. This should begin at the time of diagnosis. Ignorance inflicts often severe and possibly fatal penalties. Even when they pay a lesser price ignorance often issues to patients a pass to the surgeon whom we are now trying to avoid. Further, a little knowledge is a dangerous thing, especially when passed on from one patient to whom it may apply to another to whom it may bring disaster. Three months are necessary for the education of any patient. The time you keep him in bed is your golden opportunity. He is most anxious to learn how to avoid bed in the future. Urge him to ask questions, have him write them down. Treat him as an adult. Give him answers for whys and wherefores. Be frank but optimistic. The value of a good nurse who is familiar with pulmonary tuberculosis is inestimable. I would suggest that in any chronic disease like pulmonary tuberculosis the therapeutic triad will bring about arrest of the disease, but education alone will make it permanent.

For patients in the minimal stage it is remarkable what these apparently simple measures, when intelligently applied, will accomplish. I have already stated that among the patients discharged from the Trudeau Sanatorium

it has kept 92 per cent alive for at least 15 years. If there is any other form of treatment that produces better results I am unaware of it and am keenly desirous of hearing about it.

Furthermore, all patients with or without surgical interference, sooner or later, for a longer or shorter time, must follow such treatment. Hence the necessity for complete and accurate knowledge concerning it. Where these measures should be used is for most of these "minimal" patients of far less importance than the length of their application. The surgeons have stated that it requires little or no more time for a long than for a shorter incision to heal. Applying this to pulmonary tuberculosis I would like to emphasize that a small but definite lesion of pulmonary tuberculosis demands several years of treatment, possibly more or less modified, for a permanent arrest. Failure to recognize this and to pass it on to the patient is the most frequent cause of relapse among these early patients. Emphasize that while work may be resumed, arrest too often lingers. Tell him he may play and get well, or work and get well, but rarely can he work and play and get well.

When the patient has passed beyond this early stage the picture changes. The outlook is very different and much more serious, for the progress of the disease may now be difficult to check or such damage may already have taken place that any hope that a permanent arrest may follow the simple measures previously outlined has to be abandoned. However, granting the possibility of a successful result, so long a time is now required to bring about the desired recovery by simple means that for many it is an economic impossibility. Even for those with means the years of sacrifice of ambitions and of desires are too likely to be interspersed with periods of lapses from the straight and narrow path of tuberculosis rectitude which may lead the wanderer into the purlieus of relapse. This is the stage of disease for which surgical treatment is usually recommended and is often successful. However, not all "advanced" patients require this surgical interference but for some it must be considered immediately if their chances of arrest are not to be squandered in dangerous procrastination. I am inclined, even in the minimal group, when economic pressure is present, in the face of a continuously but slowly advancing lesion, to apply certain surgical measures. Artificial pneumothorax is, of course, included under this head.

To make myself clear, I include under the head of "advanced" patients all save those in the minimal stage. You will recall that patients in the minimal stage never have a cavity nor can the disease extend below the second rib on one side nor below the clavicles if bilateral. Of course a similar extent of disease in any area of the lung places the patient in the minimal group. In the "advanced" patients there are several conditions of paramount importance in regard to treatment. I refer first to the type of disease, proliferative or exudative; second, to the destruction of tissue, i.e., cavity; third, to the age of the patient; and fourth, to his race. The proliferative type may not force us into immediate action but the presence of an

exudative state indicates a more acute process, a more treacherous disease, that can pass at a bound from a temporizing condition into one that spells defeat or, unfortunately less often, almost as rapidly clear up. The presence of a cavity demands nice discrimination from the physician in charge of the patient. There are several important factors in this connection: First, the size of the cavity (the larger, the more serious); second, its location in regard to the pleura and fissures (the nearer, the less likely the efficacy of simple collapse); third, the condition of the wall of the cavity (absence of a wall under certain conditions is more favorable; the thicker the wall, usually the more serious is the condition); and fourth, the associated disease (the more advanced the more dangerous).

The age of the patient cannot be overlooked. Those in the " teen " ages require more careful watching, more active, more expeditious treatment. If, perchance, the patient be a girl, these requirements are emphasized. Recent studies with the roentgen-ray explain why some of these children are never seen to pass through a minimal stage of the disease. The lesion progresses under cover without exciting symptoms until such time as an acute cold or an hemoptysis draws attention to the lungs, when the disease is found to be already in an advanced stage. The only way to treat such patients is to discover them by routine tuberculin testing and roentgenography applied during their high school days. The resilience of youth favors recovery, its exhilaration lessens the chances of recovery. With increasing years relapse is said to be more frequent, recovery less pronounced, advance of the disease slower.

I have spoken of active expeditious treatment and by this I mean some form of collapse therapy. The most widely used is, of course, artificial pneumothorax. An efficient collapse by this treatment occurs in about 40 per cent of all suitable patients. About three-quarters of these achieve a permanent arrest of their disease. So of those selected for the induction of pneumothorax 30 per cent are arrested. The remaining 70 per cent should not be subjected to artificial pneumothorax for too long a time for unquestionably ineffective or contraselective pneumothorax is dangerous and may hasten the patient toward his death. Happily intrapleural pneumolysis has converted many cases of ineffective into effective instances of collapse, terminating in permanent arrest. Some have suggested that the benefits of artificial pneumothorax are bought with the price of some loss of lung function, more than is entailed in the natural cure, and while this may be so, the appalling death rate in those in whom artificial pneumothorax is tried unsuccessfully, fully justifies the procedure. It is questionable whether this form of collapse treatment shortens the time of curing but undoubtedly it does abbreviate the period of inactivity. While the number of patients suitable for artificial pneumothorax is considerable, the remainder, together with the failures, compose a large group. For these other methods of treatment must be sought.

The phrenic operation follows artificial pneumothorax closely in frequency of use. It has undoubtedly been used at times psychologically to offset the disappointment at failure of other methods. The number of these forlorn hopes is larger that some of us imagine. In carefully selected patients the results of cavity closure are encouraging. They are far better among the moderately advanced type than among the far advanced. (In my experience 62 per cent against 12 per cent.) A temporary phrenic operation removes some of the objections offered to the operation. I have been disappointed in the results obtained when I have employed it to bring about closure of a cavity in a lung partially collapsed by artificial pneumothorax. Combined with scaleniotomy or followed by scaleniotomy better results may be had in some few instances.

May I say a word about postural rest at this time. Many apparently believe that by placing the patient upon the diseased side the affected lung would suffer less. Many years ago we called attention to the fact that increased movement of the diaphragm on the dependent side compensated for decreased movement of the ribs and vice versa and, furthermore, that it was very doubtful if lying on one side decreased in any amount the respiratory function of that lung. This has apparently been recently confirmed (Pierson and Newell). If, on the other hand, the diaphragm be paralyzed, then postural rest may prove to be more efficacious. Following the phrenic operation I have used in some patients a shot bag on the chest and have raised the foot of the bed 12 inches. Some of the patients have improved. The use of weights on the abdomen, especially when the left lung is affected, and compression of the abdomen by belts, so helpful in some cases of emphysema, should be more beneficial after a phrenic operation.

A successful thoracoplasty is a highly satisfactory operation. It lingers ever in the back of the mind of both patient and physician, and in the front of the mind of most thoracic surgeons. The immediate results have been greatly improved in skillful hands. It has saved many patients from a speedy death. The ultimate results at the end of five and 10 years have been confused by the frequent improvements in technic and failure to state the condition of the patient at the time of rib removal. The operation has come to stay and it behooves all of us to become familiar with its indications. It often frees the sputum of bacilli, decreases the amount of sputum if any persists after operation, and enables a hopeless invalid to resume a normal life. I shall await with great interest to see how these patients weather the respiratory storms so common during the colder months.

There are other surgical procedures, bilateral artificial pneumothorax, oleothorax, apicolysis, plombage, intercostal neurectomy, excision of the lung, all of which have had their uses and advocates.

Before passing on I should like to emphasize the fact that none of the surgical measures which I have recommended excise the diseased area. These procedures act mechanically to put the lung more or less at rest and so to limit the poisoning, to relax the lung, and to place it finally in such a posi-

tion that the simple measures mentioned under the discussion of the treatment of the "minimal" may now become effective for the "advanced" patients.

Now since the therapeutic quadrad is apparently necessary in all instances, it is desirable to decide where it can best be put into practice. For those below a certain economic level, the sanatorium or sanatorium-hospital, rarely a general hospital, is best. The more newly constructed institutions are built really for affording rest for patients, and in them every bed is a "hospital" bed, and all the measures advocated for hastening the formation of fibrosis can be used. Many of the economically independent, under a well trained physician, also do remarkably well at home, so well indeed that change of climate, formerly so strongly advocated, is now neglected to the loss of a certain number of patients. All climates might be divided into two groups, sedative and stimulating. Why some are stimulating is difficult to say. As recovery with or without operative measures depends upon the formation of new connective tissue, increased stimulation would seem in some cases advisable. This may be had, as Dr. Trudeau long ago said, in the middle of the ocean, in the midst of the sands of the desert, or on the mountain. Many may not, as I have said, require this; some unquestionably do.

Complications of pulmonary tuberculosis are apparently growing less frequent. A satisfactory method for the diagnosis of secondary intestinal tuberculosis has been followed by numerous recoveries, after the use of heliotherapy or high vitamin diet, whereas formerly, death usually sooner or later supervened. Laryngeal tuberculosis, considered a fatal complication 30 to 40 years ago, now yields to vocal rest, electrocauterization and heliotherapy. Diabetics, after the onset of pulmonary tuberculosis, formerly usually died when put on the diet considered necessary for the tuberculosis, but now with insulin, and the diet required for the diabetes, they frequently recover. The pleural complications, not uncommon in artificial pneumothorax, and at first so dangerous, now yield to the attack by physician and surgeon. The treatment of the complication of pregnancy depends upon how the patient stands pregnancy, whether the predominating type of disease is exudative or proliferative, and how she can be cared for during and following pregnancy. In active disease, prevention of conception is to be preferred to abortion, which should not be attempted after the third month. Artificial pneumothorax may help many patients to bear one or more children safely.

Syphilis should be treated somewhat mildly while pursuing the usual treatment for the pulmonary tuberculosis.

The medicinal treatment has at present few advocates for no substance has been found that can destroy the bacilli and their contained poisons and not injure the host. The destruction indeed of the bacilli in large enough quantities would, on account of the allergic state, bring most patients to the brink of the grave or totter them into it. The only hopeful result from

chemotherapy so far has been the gold salts. In certain instances they have been found helpful. Search for a new tuberculin, which still goes on, is a confession of a present lack of the desired results. BCG, practically a preventive vaccine, is not for use in treatment. Heliotherapy and roentgenotherapy in uncomplicated pulmonary tuberculosis have afforded no convincing proof of their aid. Psychotherapy, used consciously or unconsciously, by all practising physicians, is still as important as it was in the days of Hippocrates. Occupational therapy has helped many to pass the dragging hours of rest.

Finally I would like to emphasize the thought that recovery from pulmonary tuberculosis depends not only upon what we do for the patient but much upon what he brings with him to the physician, in his head as well as in his lungs. We can assist, but do we improve upon the vis medicatrix naturae as brought about by rest, food, air and education?

TUBERCULOSIS AMONG STUDENT NURSES: A FIVE YEAR STUDY AT BELLEVUE HOSPITAL *

By J. Burns Amberson, Jr., F.A.C.P., and H. McLeod Riggins,
New York, N. Y.

This study was undertaken to collect accurate information about the incidence of tuberculosis among student nurses, to test the efficacy of a system of early diagnosis and case finding, and to measure the results of a rather rigid system of rest treatment in the cases found. Previously, like many others, we had observed a great deal of tuberculosis in nurses but could only infer its duration, rate of progression and relation to hospital service. Such inferences do not answer obviously important questions. A planned study is necessary, and this must be continued for a period of years. Because of the insidious and variable behavior of the disease, a five years' study was considered to be the minimum needed for our purposes. Accordingly it was started in February 1931.

Bellevue Hospital is a municipal institution with a normal bed capacity of 2333, in addition to an outpatient department registering 2171 visits daily. All types of cases, excepting the acute contagious diseases of childhood, are accepted. The Tuberculosis Service has 174 beds. Tuberculous patients who require specialized treatment, such as surgery, are accommodated on wards of the service concerned. Overcrowding is almost constant in Bellevue. The Tuberculosis Service, for instance, often has an excess of 40 to 100 patients, who are accommodated in cots in the center of the wards and, at unusual times, also in the corridors. In the last five years from 3100 to 3600 patients have been admitted to the Tuberculosis Service each year; 15 to 20 per cent of these cases are found not to be tuberculous. According to accepted standards, the nursing personnel is usually inadequate numerically, and at times the duties of the nurses are extremely arduous.

The nursing staff is made up approximately as follows: graduates (male and female) 625; students (female) Bellevue School of Nursing, 200; students (male) Mills School of Nursing, 67; affiliating students (male and female) 121; preliminary students (female) 45; total 1058. This study is limited to female students of the Bellevue School of Nursing. On admission to the school these women average from 18 to 20 years of age. About half come from cities and half from the country and small towns. One class enters in February and one in September of each year, the number of students in a class varying from 25 to 65. The duration of the course is three years. Upon being accepted for training the nurses see

* Presented at the Detroit meeting of the American College of Physicians, March 6, 1936.

From the Tuberculosis Service of the First Medical Division of Bellevue Hospital and the Department of Practice of Medicine, Columbia University, College of Physicians and Surgeons.

service in practically all hospital departments. The hours of duty, not including classes, are eight daily for six days a week. One month is spent on the tuberculosis service after the beginning of the second year of training. Here, as in all other departments, the nurses wear gowns when ministering to patients, but do not wear face masks. Cleanliness, especially frequent washing of the hands, is urged upon all nurses, but " contagion technic " is not employed.

Selection of Candidates. The selection of young women to undertake the arduous course of training is an important task. Up to September 1933, suitable candidates were accepted for the usual probational period, but, since then, a different and more effective plan has been followed. All candidates now spend a preliminary two weeks' " orientation period " before selections are made. During this time the Health Service of the School, under the direction of Miss Mary M. Sullivan, subjects each candidate to a rigid examination including family, social and personal history, a general physical examination, urinalysis, hemoglobin estimation, chest roentgen-ray, Mantoux tuberculin test, and a psychiatric interview. Personality, emotional stability and intelligence are studied. On the bases of the findings during the " orientation period," the women who fail to qualify physically, mentally, emotionally or otherwise are rejected.

Approximately 8 to 10 per cent of the candidates are rejected during these two weeks. The main physical reasons for rejection have been organic heart disease, established hypertension, general asthenia and tuberculosis. Among 591 candidates examined by roentgen-ray during our five years' study, seven were rejected because of the discovery of pulmonary tuberculosis. These were young women in apparently good health. The finding by roentgenogram of small nodules or scars, usually apical and presumably tuberculous, or of old calcified deposits in the pulmonary parenchyma or tracheobronchial lymph nodes was not considered reason for rejection, but parenchymal lesions of greater size were so considered, even though some appeared partly fibrotic.

Preliminary Tuberculin Testing. During the first week in the school the students received Mantoux tests starting with 0.1 mg. Old Tuberculin (New York City, Department of Health). Those who failed to react were tested during the second week with a dose of 1 mg. O.T. On this basis 312 or 57.9 per cent of 539 candidates were positive to the tuberculin test on coming to the school during the five years' period. Since September 1933, 62.9 per cent of 305 have been positive. It was found that about one-third of those who failed to react to 0.1 mg., did react to 1 mg. O.T. No doubt still more would have reacted to higher doses but probably not in such proportion. In this connection we may mention that three women with gross shadows of calcified tuberculous lesions in the lungs or tracheobronchial lymph nodes or both failed to react to 1 mg. O.T. No discrimination with regard to the results of the tuberculin testing was exercised in the selection or rejection of candidates.

Follow-Up during Training. During the first year of training an additional number (about 20 per cent) of students are eliminated from the school, usually because of scholastic failure, but, with few exceptions, the remainder finish the course successfully. Each nurse has a physical examination annually. Illness, when it occurs, is caused chiefly by acute respiratory infection. In the five years' period there was one death, caused by acute appendicitis and peritonitis. No difference was detected in the general health of the tuberculin-negative and tuberculin-positive nurses.

Subsequent tuberculin testing was performed on those negative to 1 mg. O.T. on admission to the school. In this way the incidence of new infection could be determined approximately, although, as stated, such a negative test is not absolute proof that previous infection had not occurred. Retesting was done every six months until a reaction was noted. In a group of 143 such students followed from six months to three years, and for whom we have accurate information, 37 became positive to tuberculin during their first year of training, 37 during the second year and 10 during the third. Among 70 " negatives " followed for the full three years of the course, all but 10 became positive. Thus it is seen that the majority of presumably uninfected nurses became infected some time during their course. An interesting observation was that most of these newly positive skin reactions were severe (" four plus "). No significant relationship could be discovered between the first positive tuberculin test and the character of the preceding hospital service. The Tuberculosis Service appeared no more related in this respect than other hospital departments. There was no way of ascertaining how many of these students acquired their first infection while moving among the people of New York City outside the hospital.

Tuberculosis Case Finding. In addition to the admission roentgenogram, every student nurse had a chest roentgenogram (flat film) at the end of each subsequent six months. Routine hospital technic was employed, and reëxamination ordered if the films were unsatisfactory. Comparisons were made with preceding films and, in case of the finding of any definitely or questionably abnormal changes, the student was examined and studied by appropriate means. During the six months' interval, additional examinations were done when symptoms indicated. The only important problems for differential diagnosis were pulmonary lesions in three cases which proved to be bronchopneumonia.

The important features of newly developed tuberculosis discovered during these five years are presented in the accompanying table. In short, there were eight cases including six with pulmonary lesions, one serofibrinous pleurisy, and one spondylitis. One case was diagnosed in the first year of training, three in the second and four in the third. None except the nurse with pleurisy had fever at the time of diagnosis, and the only constitutional symptoms were usually slight loss of weight and fatigue in five cases. None was aware of symptoms suggestive of tuberculosis. A few fine râles were heard in a single localized area in three of the pulmonary

TABLE I

TABLE I

Case	Diagnosis	Symptoms			Physical signs	Extent of lesion by x-ray	Mantoux test on entering school	Interval between first positive Mantoux and finding of lesion	Tubercle bacilli in sputum	Treatment	*Result* T., Still under treatment A., Arrested W., Working
		Fever	Other constitutional	Local							
New and Definite Lesions											
M. C.	Pulmonary tuberculosis	0	0	0	0	3 cm.	0	2–3 months?	0	None	A. W.
J. W.	Pulmonary tuberculosis	0	0	0	0	0.5 cm.	0	1 month	0	None	A. W.
B. D.	Pulmonary tuberculosis	0	Slight	Slight cough	Râles	4 cm. (later spread)	+		0	Sanatorium and home, 24 months	T.
A. D.	Pulmonary tuberculosis	0	Slight	0	0	2 cm.	0 (Calcified pulmonary lesion)	24 months	0	Hospital and sanatorium, 6 months	A. T.
H. W.	Pulmonary tuberculosis	0	0	0	Râles	2 cm.	0	13 months	0	Hospital and home, 12 months	A. W.
R. M.	Pulmonary tuberculosis	0	Slight	Slight cough	Râles	2 cm.	0	13 months	+	Hospital and sanatorium, 12 months	A.
M. P.	Potts' disease	0	Slight	Back pain	Tenderness	One lumbar vertebra	0	1 month (first symptoms)		Hospital 5 months, spinal fusion	T.
G. S.	Serofibrinous pleurisy	Up to 100°	Moderate	Pain chest, cough	Signs of effusion	Moderate effusion	+			Infirmary and home, 5 months	A. W.

TABLE I—*Continued*

Case	Diagnosis	Symptoms			Physical signs	Extent of lesion by x-ray	Mantoux test on entering school	Interval between first positive Mantoux and finding of lesion	Tubercle bacilli in sputum	Treatment	*Result* T., Still under treatment A., Arrested W., Working
		Fever	Other constitutional	Local							
Preëxisting Lesions											
C. B.	Pulmonary tuberculosis	0	0	0	0	0.5 cm. (slight increase in lesion present on admission; later receded)	+		0	None	A. W.
R. B.	Tracheobronchial lymphadenitis	0	Moderate	0	0	Moderate enlargement in region of old partly calcified lesions	+			Home 3 months	A. W.

cases; the other three presented no abnormal signs. None had sputum of any significant amount, and tubercle bacilli were not demonstrated in specimens obtained. Thoracentesis yielded clear serous fluid in the case of pleurisy. The diagnosis of tuberculous spondylitis was made in one case by the orthopedic surgeons on the basis of low back pain and tenderness lasting for three months and the roentgen-ray demonstration of narrowing of an intervertebral space.

The diagnosis of the six pulmonary lesions was made chiefly by roentgenogram. In none of these was the diagnosis suggested by the findings six months previously. The lesions discovered were all presumably of a fresh exudative type. The largest extended from the apex to the second rib on the right and the smallest appeared as a density about 0.5 cm. in diameter. (The diagnosis in this case is questionable, but we include it as being presumably tuberculous.) In the other four the lesions averaged about 2 cm. in diameter, appearing as soft cottony localized patches in the roentgenogram. No cavities were demonstrated. The classification in all cases was Minimal A.

Two additional cases are tabulated in which temporary extensions of old lesions occurred. In one the lesion was a tiny nodule in the pulmonary parenchyma which increased to about 0.5 cm. in diameter and then, by the end of a year, receded to its original size. In the other, a rather marked enlargement of the tracheobronchial and mediastinal lymph nodes, with the symptoms of weight loss and fatigue, occurred. This woman had a number of partly calcified lymph node lesions in this region and also in the cervical region on admission to the school. The swelling subsided within a year, and she has been well and working for a year.

Treatment and Results. In two cases with small pulmonary lesions no treatment was advised, and healing has taken place under observation; in one, the tiny focus can no longer be identified. In three other pulmonary cases, strict bed rest was given for two to three months followed by partial rest at home, in one case, and in a sanatorium, in two. The lesions are arrested and healing. In one case, in which bed rest was advised but omitted, an extension of the lesion occurred, but this patient is reported improving under treatment. The nurse with serofibrinous pleurisy recovered completely after five months of bed rest and convalescence and has been working for 18 months. In one case tubercle bacilli were demonstrated in the sputum during treatment.

In these cases, therefore, the lesions were arrested and healed or healing in six and improving in the seventh. No form of collapse therapy has been needed. The nurse with tuberculous spondylitis has recently (February 1936) had a spinal fusion operation and the prognosis is favorable. There have been no deaths from tuberculosis.

Relationship to Tuberculin Sensitiveness. Among these freshly developed cases, the Mantoux test as the nurses entered the school was positive in two and negative in six, but in one of the six a calcified tuberculous

focus about 1 cm. in diameter was demonstrated by roentgen-ray. If we supplement this small series of cases with observations we have made among other nurses at Bellevue, we do not find any definite trend. In other words, the occurrence and behavior of tuberculosis in all nurses coming under our observation thus far have not varied significantly in relation to the results of preceding tuberculin tests. It should be noted that no freshly developed lesions in the tracheobronchial or mediastinal lymph nodes were demonstrated in those who became tuberculin-sensitive under observation.

Observation after Graduation. This study does not include any methodical case finding among the nurses who have graduated from the school. However, the 135 who have graduated in classes included in the study are almost all employed in the hospital and we have their general health records from six months to two years after graduation. During this time one new case of "minimal" pulmonary tuberculosis has been found among the 135 graduates. Two others have had one attack each of erythema nodosum; both have recovered and neither has shown any evidence of tuberculosis. Since the etiology of erythema nodosum is disputed we do not include these among our definite cases. We have no evidence to lead us to believe that the occurrence of erythema nodosum favors the later development of tuberculosis.

Tuberculosis Case Rate. Because of the relatively small size of the group included in our study the morbidity rate from tuberculosis during these five years cannot be expected necessarily to represent a definite trend. Another five years' observation will establish this more accurately. Excluding two cases in which the observed changes certainly indicated temporary inflammatory reactions about previously established lesions, the eight cases in which we detected newly developed lesions represent 1.6 per cent of 492 young women who entered the school as students. However, because of variations in the length of observation, these figures have little meaning. The experience is better expressed as follows:

A total of eight nurses developed new tuberculous lesions during the course of training, representing a case rate of 1.09 per 100 nurses per year.

Seven of these were lesions of the lungs or pleura, or 0.95 per 100 per year.

Five of those with pulmonary or pleural lesions required treatment, or 0.68 per 100 per year.

Enumeration of cases, alone, is misleading, especially when the lesions are small, because it affords a very inadequate idea of the actual seriousness of tuberculosis in any group. In six of these eight cases, the lesions have healed or are healing well with or without treatment. According to sanatorium experience, the expectancy of health and life in these six should be very close to normal. In the remaining two (one pulmonary case and one spondylitis) still under treatment the disease may be said to constitute a serious threat, although the prognosis at present seems to be favorable for eventual recovery. Including the three cases under treatment and basing a

tabulation on the entire group of student nurses included in the study, it is indicated that the loss of time on account of tuberculosis during the five years was 2.7 days per nurse per year.

Other Bellevue Nurses. It has been shown that tuberculosis in Bellevue student nurses was discovered mainly by regular roentgenographic examination of the chest before the pulmonary lesions had progressed beyond a "minimal" stage, before excavation had occurred, and before definite symptoms had developed. The great value of such a case finding procedure is proved by contrasting our experience with other groups made up of graduate and affiliating student nurses at Bellevue. These groups did not come within our study, and consequently reported for examination as a rule only when they had definite symptoms. Graduates, of course, were more aware than affiliate students of the insidious character of symptoms of tuberculosis. In six years we have discovered tuberculosis in 26 nurses from these two groups. Five had pleurisy with effusion alone. Among graduates we discovered seven minimal lesions, six moderately advanced, and two far advanced; among affiliates, none minimal, five moderately advanced and one far advanced. In both groups, therefore, the lesions were in a moderately or far advanced stage in 67 per cent of the cases when the nurses first developed symptoms sufficiently impressive to indicate to them the need of an examination. This coincides with the experience in the tuberculosis clinics in New York City and in practice generally.

Costs. The cost of finished roentgen-ray films for the Bellevue school enrollment was about $500 a year. Other costs were absorbed in the general functioning of hospital departments and the Health Service of the school. The results, if measured in terms of early diagnosis and prevention of chronic disabling illness, fully justify the expenditure. Economically, it must be considered that early diagnosis saves many thousands of dollars by shortening the period of treatment and restoring nurses to almost full working capacity. One Bellevue graduate, employed in the operating room, was found to have advanced bilateral pulmonary tuberculosis when symptoms first led her to report for examination. She received treatment for five years at a cost of at least five thousand dollars, and at the end of five years she died.

Comment

The experience indicates that student nurses entering Bellevue Hospital with negative tuberculin tests became tuberculin sensitive at a rate somewhat in excess of that which would be anticipated in the general community. This observation alone, however, does not suffice to measure the hazard of clinical tuberculosis in relation to that which prevails for the community at large. It must be considered, as Dublin [1] finds, that the tuberculosis death rate among white females in the general population ascends to its peak in the 20 to 24 age group. Likewise, there is customarily a striking accretion of new pulmonary lesions. Fellows [2] reports an incidence of new

lesions of clinical importance among 4000 female employees, aged 18 to 22, in the home office of the Metropolitan Life Insurance Company in New York City, amounting to 0.25 per hundred per year. This rate, established by observation of the group from January 1932, until June 1935, applies to cases in which treatment was usually indicated. In our group the case rate was approximately 0.68 per hundred nurses per year of new pulmonary or pleural lesions requiring treatment, but the incidence of all new lesions was 1.09. The comparison of rates alone, however, is not valid for the following reasons: (1) Our group is small and later observation may reveal a different trend of morbidity; (2) Our cases were found by roentgenogram which is known to reveal more small lesions than the fluoroscopic method which Fellows and his coworkers employ; (3) Tiny pulmonary lesions may appear and recede to insignificant dimensions within a year, and a semi-annual roentgenogram will occasionally reveal one of these which would be missed by an annual fluoroscopy; (4) Fellows' statistics do not include tuberculosis outside the lungs and pleura; (5) Other factors, such as racial stock and time for adaptation to city life, are not considered.

During 1935 the days lost from work on account of tuberculosis by Metropolitan Life Insurance Company home office employees, aged 17 to 35, was 2.6 per female per year. The similarity of our average of 2.7 per nurse per year during the five years' period is interesting, therefore, even though we draw no conclusion from the comparison.

Age distribution of new cases is not known for New York City, but with a death rate of 85, it may be assumed that at least 170 new cases of tuberculosis per 100,000 females in this age group are reported to the Board of Health annually, that these are almost all symptomatic cases, that they are cases of advanced disease in at least 70 per cent of the instances, and that they represent only a fraction of newly developed lesions. Therefore, while we have no basis of comparison for all newly developed lesions, it is clear that, with the system of case finding and control described, the hazard of serious and advanced tuberculosis for Bellevue student nurses has not exceeded that for young women pursuing other occupations in the City.

During the past six years, 50 young physicians have served as resident physicians or interns, some for six months and most for at least one year, on the Tuberculosis Service. Two, both women, are known to have developed clinical pulmonary tuberculosis. In one case this was an extension from a fibrotic lesion which was present when the physician came to the Service; in the other, fairly large apparently calcified lesions in the lung and tracheobronchial lymph nodes were identified previously.

In considering this problem as it concerns the nursing and medical profession generally, further methodical studies are needed on which to base fair judgment. It is to be anticipated that the incidence of tuberculosis will continue among nurses who have graduated but, thus far, we have not proved it to exceed the expected community rate. In a recent analysis of death rates by occupation, Whitney [3] finds that the standardized mortality

rate from tuberculosis of the respiratory system among male physicians and surgeons in 10 selected states was 23.7 per 100,000 in 1930. This compares with a mortality of 175.3 among all gainfully occupied males, 15 to 64 years of age. Next to lawyers, judges and justices, with a rate of 18.3, physicians and surgeons enjoyed the lowest rate among all gainfully occupied males in these states.

Our study demonstrates anew the remarkable tolerance of adult human beings for infection with the tubercle bacillus, even in an environment where the opportunities for infection are great. It is again apparent that infection is only one factor in the combination which makes for clinical tuberculosis, though it is obviously the necessary one. It is, of course, highly desirable to avoid infection if possible, but at present this is not wholly possible either in Bellevue Hospital or elsewhere in New York. Other safeguards against the development of serious, chronic, disabling and fatal tuberculosis should be set up not only in nursing schools but also among other groups, particularly among young people generally. Methodical case finding in such groups will almost always detect the presence of tuberculosis in its earliest clinical phase—the only phase in which the disease can be considered curable in 80 to 90 per cent of the cases.

Conclusion

During the past five years tuberculosis among nurses in the Bellevue Hospital School of Nursing has been controlled so that its seriousness as a disabling and fatal disease does not appear to exceed that expected among young women in other occupations in New York City.

We wish to express our thanks to Miss Mary M. Sullivan, Director of the Health Service of the Bellevue Hospital School of Nursing, for her assistance and coöperation. Acknowledgments are also made for the coöperation of Dr. Clarence E. de la Chapelle, physician to the Health Service, and for the interest and suggestions of Dr. Haynes Harold Fellows, Assistant Medical Director of the Metropolitan Life Insurance Company.

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THE DIAGNOSIS OF SILICOSIS, WITH SPECIAL REFERENCE TO ROENTGENOLOGICAL MANIFESTATIONS *

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BECAUSE conditions caused by the inhalation of dust are so frequently involved in litigation it is necessary that they be defined with the greatest clarity. Our terminology developed forty to fifty years ago, before the pathology of such conditions had been worked out. Pneumoconiosis was the term coined to designate disease of the lungs due to inhaled dust, regardless of its nature. Anthracosis, siderosis, chalicosis, silicosis were specific forms of pneumoconiosis due to inhaled coal, iron, stone dust and silica respectively. All were considered of equal significance as it was believed that any dust was merely a foreign body which, when inhaled in excess, would produce scar tissue. Then came the discovery that silica was different; that it acted like a poison and caused a specific and progressive fibrosis. If the inhalation of iron or coal dust caused damage it was because they were mixed with appreciable quantities of silica. Other dusts, with the exception of the silicate, asbestos, were apparently quite harmless. The search for still other dangerous dusts is being continued but thus far none has been discovered.

The original terminology is firmly fixed in the literature and it is still valuable if it is used intelligently, but not all medical men are yet familiar with these more recent discoveries, and non-medical persons are apt to be confused by the implications of the terms. It would seem preferable to use the term, silicosis, for progressive disease of the lungs produced by inhaled silica dust. If, in addition, the lungs happen to contain significant quantities of coal or iron the compound terms, anthraco-silicosis or sidero-silicosis, are descriptive. Inhalation of relatively pure coal or iron produces no change that should be interpreted as a disease process. They cause pigmentation but this is disease only in the same sense as the callouses on the palms of the hands, or the pigmentation of the skin from prolonged exposure to the sun. Such changes are in a strict sense pathological but they do not interfere with function and are therefore not ordinarily classified as diseases.

For the same reason the writer would prefer to abandon the use of the term, pneumoconiosis. Its implications are too broad; it connotes a *disease* process when actually its user may have in mind a benign pigmentation of the lungs with or without slight proliferative changes. It is sometimes a convenience to the pathologist in making an anatomical diagnosis of a condition due to some dust whose action is not yet defined. It is also a convenience to the roentgenologist, but he cannot see the dust in his shadows as the pathologist can in his sections. Far too frequently the film is labeled " pneumoconiosis " because of a history of dust exposure. To the

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non-medical mind the term means disease with as serious consequences as silicosis. If it is to be retained, pneumoconiosis should be defined as a *condition* of the lungs resulting from the inhalation of dust that may or may not be of clinical significance.

This paper will point out the specific nature of the reaction to silica; it will attempt to show that no other dust, with the exception of asbestos, is known to produce significant amounts of fibrous tissue in the lungs. It will also indicate the important relationships between silicosis and tuberculous infection.

Space will not permit a review of the numerous observations leading to the conclusion that silica is unique among inorganic materials in exciting a progressive fibrosis of the tissues. It must suffice to state that the injection of a suspension of minute silica particles produces a localized acute inflammatory response associated with phagocytosis by mononuclear cells. This is followed by necrosis and subsequent repair characterized by the formation of a nodule of swollen, hyalinized connective tissue fibers. The finer the particles the more rapid the response of the tissues. Within limits the reaction is a progressive one but, being nodular in type, progression is manifested by a slow increase in size of the original area of involvement. Injection of the same amount of the same sized particles of non-siliceous substances like carborundum, emery, diamond, coal, iron oxide, etc., causes a transitory inflammation with phagocytosis but the lesion is not nodular; it is followed by no necrosis, only a few connective tissue cells are formed and none of them form hyaline fibers.

Many observers are of the opinion that the silica particles dissolve and thus poison the tissue, but this contention cannot be proved by chemical methods. Indirect evidence would seem to substantiate this view but silica, or quartz, is only very slightly soluble at the hydrogen-ion concentration and temperature of the body. Reaction to injected silica occurs within an hour or two, which is difficult to reconcile with the solubility hypothesis. The writer believes that silica is a tissue poison but that some property other than solubility is responsible for its irritating effects.

Guinea pigs and other animals made to inhale pure silica dust for eight hours a day, over a period of a year or more, develop nodular fibrosis of the lungs that is quite comparable with the lesions found in human beings with silicosis. Their disease begins with phagocytosis of the dust particles in the air spaces, migration of these dust-containing cells into the lymphatic system, and concentration of the foreign bodies in the areolar tissues along the vessels and at focal points in the lymphoid tissues. Proliferation of the local connective tissues follows, producing perilymphatic sheaths of fibrosis and tubercle-like nodules of fibrosis in the lymphoid tissues. Because of their position the expanding nodules tend to compress the adjacent lymphatic vessels. The free flow of lymph from the lung is impeded and subsequently inhaled dust is more apt to remain in the air spaces.

With the drainage system of the organ impaired the phagocytes tend to carry dust particles into the walls of the air spaces. Proliferation of the connective tissues in this location causes both nodular and diffuse fibrosis. The latter is more prone to occur when the dust concentrations are high and the foreign bodies accumulate much faster than they can be removed by physiological mechanisms. The nodular foci of reaction exhibit the same evolution as that described for injected silica. If the dust accumulates slowly, necrosis is slight and may involve only a few cells at a time; if it accumulates rapidly necrosis may dominate the picture. In rabbits, and sometimes in guinea pigs and human beings, necrosis is ultimately replaced by calcification.

Inhaled mineral *particles* other than silica are phagocytosed by the same kind of cells and many of them removed to the lymphatic system. There is a decided tendency for some of the phagocytes to become overloaded so that their motility is impaired and they remain with their ingested material inside the air spaces. Since much of the dust makes its way to the alveoli beneath the pleura, the surface of the lung is pigmented if a colored dust is involved. These mineral particles do not actively stimulate connective tissue, and no appreciable proliferation occurs. After one or two years of exposure to heavy concentrations of such dusts one finds accumulations in the superficial air spaces, in and along the lymphatic trunks that course through the walls of the vessels, in the lymph nodules inside the lung, and in the lymph nodes at their roots. Such deposits stimulate only the very slightest proliferation of connective tissue. From its location such reaction can hardly affect pulmonary function.

Animals breathing the *fibers* of the silicate, asbestos, show a third type of reaction. A considerable number of these fibers are able to pass the barriers of the upper respiratory tract and to slip along over the surface of the ciliated epithelium lining the bronchi. When they reach the sacculated walls of the respiratory bronchioles they are caught in the lateral alveoli and practically none are carried onward into the terminal air spaces. This type of foreign body seems to present a new and difficult problem to the defense mechanisms. Phagocytes and giant cells attempt to ingest the fibers but they are apparently unable to transport them. Most of the cells remain in and along the walls of the terminal bronchioles where they first lodged; only very rarely can fibers be found in the lymphatic system. In the presence of complicating infection a few may be transported to the lymph nodes.

All of the reactions to fibrous asbestos thus far observed have been confined to the region of the terminal bronchioles. The reactive process starts as a collar of cellular fibrosis about these structures and during a three year period of exposure the only appreciable extension has occurred peripherally along the alveolar ducts given off from the ends of the bronchioles. The ultimate alveolar sacs and alveoli are uninvolved and no reaction is detectable in the lymphatic system. The resultant picture is that of small, isolated patches of fibrosis lying in an otherwise normal lung. The characteristic

asbestosis bodies that are found in human beings are reproduced in guinea pigs. Rabbits have not developed them because their upper respiratory mechanisms are apparently adequate to prevent the penetration of fibers. Their lungs showed no fibrosis.

Only these three general types of reaction have thus far been discovered. The silicosis picture may be modified when the dust causing it contains varying quantities of non-siliceous substances like coal and iron. Under such circumstances the adulterant dust particles are not so uniformly segregated in the superficial air spaces and in the vicinity of the lymphatic system. Many of them are carried to the periphery of the silicotic nodules where they, and some of the silica, are responsible for the formation of an irregularly radiating zone of thin fibrous tissue. This disturbs the usual compact nodular arrangement of the typical silicotic lesion. The matter of protection against silica by adulterant dusts is still under investigation and cannot be discussed here. It is possible that other types of reaction, as unusual as that to asbestos, may sometime be discovered, but thus far only the three that have been described are recognized.

The effects of inhaled silica, asbestos and non-siliceous dusts upon tuberculosis have been tested in experimental animals by administering a primary inhalation infection with attenuated tubercle bacilli. In normal guinea pigs such infection causes a self-limited lesion comparable to the primary complex in man. A year or two after infection most of the tubercles have healed and largely disappeared. In silicotic animals such infection, administered at the time when the dust exposure begins, produces a chronic progressive tuberculosis that usually kills after a period of 18 months to two years. If the infection is introduced when the silicosis is fully developed the animal dies in from one to three months. Inhalation of silica instituted after the infection, when most of the tubercles are healing or healed, causes reactivation and spread from any foci that still harbor living bacilli.

In the case of asbestosis, infection, after the disease is established, runs practically the same course as that in normal control animals. Infection simultaneous with the onset of dust inhalation shows no unusual effects for six to eight months. Then it begins to spread locally in about one-half of the animals; in the others there has been no appreciable effect. Where spread occurred the process was fatal in a few instances, but in animals that survived the acute stages healing and fibrosis were the ultimate outcome. With inert dusts the infection runs a normal course if it is administered when the dust exposure is started. If it is given after some months of dusting it subsequently heals and either resolves or leaves more scar tissues than usual.

These experimental observations have been valuable in interpreting the terminal stages of various human pneumoconioses seen at the autopsy table. They, with the occasional case dying of accidental causes after short exposure, and a large amount of roentgenographic material, have made it

possible to build up pictures of the evolution of these conditions in man. In considering this phase of the subject the roentgenogram will be taken as the point of departure. The various shadows seen in different forms of pneumoconiosis will be explained in the light of known pathological reactions.

In silicosis, the first pathognomonic shadow is that of the fine nodule in the parenchyma of the lung field. Such shadows are discrete, sharply circumscribed, never more than 6 mm., and usually not more than 2 or 3 mm. in diameter, and uniformly distributed throughout both lungs. The inhalation of silica produces other changes before parenchymatous nodulation develops but such changes are not specific and they are readily confused with the reaction to non-siliceous dusts. They consist of an accentuation of the linear markings of the lung due to reaction in and about the lymph trunks traversing the walls of the blood vessels. Perfect stereoroentgenograms may reveal the minute silicotic nodules in the intrapulmonary lymphoid tissues that are situated at the bifurcation of blood vessels. There may also be enlargement of the mediastinal shadow due to the reaction to the silica brought to the tracheobronchial lymph nodes. But such changes are not specific; they may be caused by pulmonary infection. The linear exaggeration is equally well produced by the inhalation of non-siliceous dusts. Therefore, even in the presence of a history of several years' exposure to silica dust, one is not justified in diagnosing silicosis unless he sees the characteristic nodular shadows in the lung fields.

In addition to generalized discrete nodulation, simple silicosis may exhibit massive conglomerations in localized areas of the lungs. The shadows of conglomerate lesions are frequently seen in films of persons exposed to mixtures of silica and other substances like coal. It seems probable that such reaction develops in areas where the lung tissues have been injured by previous infections that have subsequently healed. As the result of the injury more dust, and consequently more fibrosis, occurs in the localized area. Individuals with such pictures have no symptoms of active infection, although they are usually quite dyspneic. Serial reëxamination over a period of years reveals no change in the character of the pulmonary shadow.

When tuberculosis is superimposed upon silicosis it may manifest itself as simple superimposition or as a new type of disease known as silico-tuberculosis. The *primary complex* of tuberculosis can be detected on a background of generalized nodulation. The silica rarely has any effect upon these foci as they are generally sterile by the time persons begin to work in dust. Very rarely they have been reactivated and spread in a manner similar to that described in the guinea pig. The scars of healed *apical tuberculosis* are recognizable in the silicotic lung. After prolonged exposures to dust such lesions have been seen to break down and give rise to very chronic silico-tuberculosis, a conglomerate type of disease, that spreads slowly from the vicinity of the original focus harboring bacilli. This lesion is productive rather than exudative in character; cavity formation, if it occurs, is

a late manifestation. *Aspiration and bronchogenic* spreads to remote portions of the lungs are limited. The sputum is usually negative until late in the disease. Clinical symptoms of intoxication are slight. Silico-tuberculosis is much more commonly found in the base of the lung than simple tuberculosis. Whether the basal lesion of the silicotic is a manifestation of exogenous reinfection or whether it originates from reactivated latent foci has not been determined.

The focus of silico-tuberculosis may be difficult to differentiate from the conglomerate focus of simple silicosis, but the former being due to an active infection is constantly, though slowly, changing and its bearer will be apt to manifest some clinical evidence of it. Repeated examinations by all available methods are essential for a diagnosis.

Miliary tuberculosis occurs as a terminal event but it is particularly difficult to detect in the roentgenogram showing generalized discrete nodulation.

Pneumonia may complicate silicosis but whether it is any more frequent than in normal populations is debatable. Probably the same factors that favor its development in others are operative in the silicotic. If it occurs, failure of resolution and resultant organization are probably more frequent in the presence of complicating silicosis.

The roentgenographic picture of non-injurious dust reactions has already been mentioned. It is essentially characterized by an increased density and prominence of the linear shadows of the blood vessels in the lungs. This is due to the thickening of their walls from reaction around the lymphatic vessels that they include. There may also be a fine reticulation in the periphery of the lung from reaction about the lymphatics that course through the pleura and interlobular septa. Whether accumulations of dust in the subpleural alveoli intercept enough roentgen-rays to cast a shadow is still debated. It seems doubtful. Healing of an infectious process in a lung containing large quantities of any kind of dust is apt to be less perfect than that in a normal organ. If the infection has been widespread it may leave confusing residua that may be wrongly ascribed to the action of the dust. Such faulty interpretation can be avoided by the study of a sufficient number of persons, exposed to the particular dust in question, to establish a proper standard of comparison.

The pathology of asbestosis in the human subject needs further investigation. Present knowledge is based upon the terminal stages seen in a relatively small number of postmortem examinations. In many of these cases death has occurred from pulmonary infection, which further complicates the picture. Roentgenograms of living tuberculous subjects generally seem to depict a less severe type of reaction than that found in the "uncomplicated" case at the autopsy table.

The roentgenogram of moderately advanced asbestosis is usually characterized by a diffuse "ground glass haziness" throughout the lower parts of the lung fields. As the disease evolves, the haze spreads and the upper portions are involved. In advanced stages there is a generalized, fine

speckling throughout the lungs. The shadows simulate very fine nodulation but they are smaller and less clearly defined. In addition there is sometimes evidence of chronic pleurisy and there may be heavy linear shadows radiating from the borders of the heart. The latter are responsible for a condition labeled " the porcupine heart."

It is not yet clear whether asbestosis in the human being develops in the same fashion as the experimental lesions in guinea pigs. The detection of occasional masses of fibrosis about terminal bronchioles suggests that it does, but in all of the seven human cases that the writer has thus far had opportunity to study there have also been other and more complex fibrous reactions. If one may speculate on the probable pathological reaction responsible for the shadows seen in the roentgenogram, one would infer that the diffuse haziness of the lower lung in moderately advanced disease is caused by the superimposed shadows of innumerable collars of reaction about small terminal bronchioles. It is frequently asked why the first manifestations should appear in only one part of the organ. Probably all portions receive an equal share of inhaled particles if one can trust the appearances seen in human and animal autopsies. The writer's confrere, Dr. H. L. Sampson, has suggested that in the thicker layer of tissue penetrated by the roentgen-ray at the base of the lung there would be so many more of these fine lesions that they would cast a shadow, whereas in the thinner upper lung there would not be enough of them to intercept sufficient rays to cast a visible shadow. As these peribronchiolar foci of reaction grew larger and more fibrous with advancing disease they would become more dense and cast definite shadows. The shape of such shadows would vary with the angle of incidence of the rays upon the different lesions; some would appear as rounded spots and others would be elongated. This would explain the fine irregular stippling seen in more advanced cases. The pleural thickenings and linear shadows radiating from the borders of the heart find no explanation in the disease thus far produced in guinea pigs. It is of course possible that longer exposure might cause further changes in the lungs but thus far there has been no hint of such change, unless the asbestosis was complicated by infection. The small amount of human material that the writer has studied also suggested that healed infection was responsible for much of the fibrosis observed. However, this conclusion is provisional and may be modified when further observations become possible.

The incidence of tuberculosis complicating asbestosis is variable in different parts of the world. In Great Britain, Merewether [1] reports 35.7 per cent, in cases that have died, against 59.4 per cent for silicosis. Gloyne [2] found 17.5 per cent. In this country, Lanza, McConnell and Fehnel [3] found only one active case of tuberculosis in 67 cases of silicosis examined by roentgen-ray (1.5 per cent); seven cases showed healed tuberculous lesions. In guinea pigs, it will be recalled, asbestos dust seemed to create some tendency for tuberculous infection to spread but the effect was usually

transitory and was not manifested in all animals. Healing was attended by excessive fibrosis.

Summary

Regardless of the history of exposure to dust, a diagnosis of silicosis should not be made until generalized discrete nodular shadows are visible in the lung fields. Large localized shadows suggest complicating infection but there is a conglomerate type of simple silicosis that occurs in the absence of active infection. It may result from pulmonary damage by previous infection that has healed. It can only be differentiated from active infection by careful clinical study and by repeated roentgenograms to exclude change in the character and size of the lesion. The silicotic lung may exhibit the usual manifestations of tuberculosis, superimposed upon a background of generalized nodulation; more common are the massive foci of consolidation due to silico-tuberculosis. These may be situated in the upper parts of the lung where they result from reactivated apical foci of tuberculosis but frequently they occur in the mid or lower lung. They consist of a very chronic combination of tuberculosis and silicosis progressing simultaneously in the same area. They give rise to much less pronounced symptoms of intoxication than tuberculosis alone. More acute forms of tuberculosis, aspiration disease, and miliary tuberculosis occur but they are not very common.

Non-siliceous dusts are generally responsible for an exaggeration of the linear markings of the lung. As far as known the slight perilymphatic reactions responsible for them do not interfere with pulmonary function and they do not alter the native susceptibility to tuberculosis.

Asbestosis is not so well understood. The roentgenogram shows a diffuse haziness of the lower lung fields and later a very fine uniform stippling. Whether chronic pleurisy, increased linear markings and conglomerate shadows are due to the dust, to secondary changes incident to collapse of lobules, or to complicating infection, has not been definitely settled. The appearance of a tuberculous lesion in the asbestosis lung is apparently not modified. There may be some tendency toward chronicity.

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SILICOSIS FROM THE PUBLIC HEALTH AND ECONOMIC VIEWPOINT*

By A. J. Lanza, M.D., *New York, N. Y.*

Silicosis is essentially a chronic progressive disease, characterized by an extraordinary tendency to tubercle infection. It occurs only as an occupational disease, and the industrial processes associated with exposure to silica dust vary widely and are distributed over many dissimilar industries.

The time factor in silicosis is a lengthy one. This, together with its progressive nature, tends to complicate and confuse our efforts to deal with the silicotic patient either when he is an applicant for compensation benefits or the subject of litigative or legislative procedure. Obviously, the rate of development in a disease caused by the inhalation of dust is determined by several factors. There are the amount of free silica in the dust, the amount of dust in the atmosphere, and the extent of exposure of the individual. We estimate the severity of the hazard in any given case by weighing these three factors.

Where the amount of free silica in the dust is very high—80, 90, or 95 per cent—and the quantity of dust excessively large and the exposure constant, then the physician sees the severe or, as Gardner has termed it, the classical form of silicosis, which develops in from five to ten years, progresses steadily, and almost inevitably is complicated with a tubercle infection which runs its course fairly rapidly. This is the type of silicosis described in the early literature and found especially in mines where the rock was highly siliceous and drilling was done dry and no adequate preventive measures were enforced—a type of silicosis which is disappearing and will soon be relatively infrequent in this country.

Spread throughout industry are many dust hazards in which the combined weight of the three factors is less than under the conditions just described—the amount of silica may be relatively low—15 to 50 per cent—the quantity of the dust may not be so excessive, the exposure may be less constant, and more or less effective efforts at dust control may be attempted. In this situation, the clinical picture is one of very slow development, made evident only in the higher age groups, with little disability in the absence of infection, and a less pronounced incidence of tuberculosis.

In between the very severe and the mild types of silicosis are many gradations, resulting from the emphasis or lack of emphasis of one or more of the factors mentioned. I desire to stress the importance of establishing and evaluating these causative factors in every case of silicosis. The failure to do so has been largely responsible for much of the misapprehension and

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confusion that have characterized attempts to deal with the silicosis problem during the last few years.

The extent of the exposure to the silicosis hazard is greater than might be supposed. The following figures are quoted from a study of the subject by Vane and the author.[1] We estimated that there are about 115,000 miners in metal mines and coal mines exposed to silica dust—by no means all of the men employed in these industries. Workers in smelters, foundries, glass works, together with those employed as grinders, sandblasters, and vitreous enamelers, would account for about 325,000. Including also various other occupations with a known silica hazard, we arrived at a total of not less than 500,000 workers exposed to silicosis in this country and this, in our opinion, is a very conservative estimate.

At any rate, the burden of silicosis, both in sickness and in cost, is staggering. From the viewpoint of public health and preventive medicine, it is a shining target to shoot at. The situation is not new. What is new is the attention that has been focused on pulmonary dust diseases in the last five years, with the consequent tendency to include silicosis among the compensable diseases. The difficulties of applying the principles of compensation to an insidious and chronic disease are apparent. It is not my purpose to discuss them here. But it would seem that if these vexatious difficulties are to be overcome, a competent medical board should be an integral part of the compensation mechanism. It is, perhaps, too much to hope that there should be uniformity in the practice of the different States with respect to a standardized diagnostic procedure, but unless competent medical assistance can be made available in carrying out the provisions of occupational disease compensation laws, they cannot be administered with justice nor with a proper regard for the public interest.

The control and prevention of silicosis is, in the main, a medical problem. Upon the physician falls the responsibility of accurate and precise diagnosis—first, to determine whether the applicant for work, where a dust hazard may be present, is free from pulmonary or other disease which should bar him from such employment; and second, to discover as early as possible the indications of harmful effects among those employed. As a judge, deciding who should or who should not work in any given occupation, where an occupational disease hazard is involved, the physician renders a service to the public health as important and exacting as any professional function he may be called on to fulfill. I dwell upon this because it seems inevitable that the physician is going to be interjected into the industrial picture to an increasing extent. While it may be desirable to set up standards of employment in this matter of occupational disease hazards, such standards must be very general. There is no substitute for the personal judgment and experience of the physician, coupled with a first hand knowledge of working conditions. Each individual is a case in himself, and social and economic conditions may demand consideration as well as his physical condition.

The mitigation of the dust hazards falls within the realm of the engineer but the proof of the efficiency of engineering control methods must be determined by the presence or absence of specific pathological changes in the individuals involved. In any situation where silica dust may be a hazard, the information we seek is the percentage of silica in the dust and the number of million particles per cubic foot of air in the working place. The method of sampling and analyzing dust air in working places has been standardized by the United States Public Health Service and the United States Bureau of Mines. Their technic has been generally adopted by competent investigators. The air sample is taken with the Greenberg-Smith impinger, large samples averaging about 100 cubic feet being secured on a level with the workman's face and at a rate approximating that of normal breathing. The sample is analyzed for free silica, and from microscopic preparations the particles are counted and the size-frequency determined. Under most industrial conditions, about 90 per cent of the particles are under ten microns in size. While dust determinations do not come within the physician's duties, he should be able to evaluate the information obtained, otherwise he cannot determine who should be employed and who should be rejected, nor who should be transferred to another job, and who retained.

Workmen exposed to a silica hazard should be examined periodically. An annual examination may be sufficient but the judgment of the physician must be the deciding factor and he should have the right to reëxamine those under his care as often as he deems advisable. When a workman is found to have silicosis, he should be protected from further dust exposure—if necessary transferred to another job. When a silicotic becomes tuberculous, he should be placed upon complete disability, both in his own interest and that of his fellow workmen.

From the point of view of diagnosis the value of the roentgenogram has been stressed. While it is true that a roentgen-ray film of the chest is essential, it should be recognized that there is a tendency to disregard other necessary and important diagnostic information. It is a common occurrence for films to be sent to our office for confirmation of a diagnosis with no case history or clinical data whatsoever. A complete occupational history, as well as a clinical history, and a thorough physical examination are necessary if the film is to be correctly interpreted. It is also vitally important that the physician who attempts the diagnosis of silicosis be familiar with the general appearance of chest films of working men so that he may be conversant with the various appearances that are compatible with what has been aptly termed "the healthy chest."

The attention that has been centered upon the various pneumoconioses in the last few years has revealed the tendency to disregard occupation as one of the important factors in the clinical history of patients who come from the wage earning class. It is unusual to find an accurate occupational history in either private or institutional records, which is one of the reasons why occupational diseases are not diagnosed more frequently. Espe-

cially where the disease is essentially chronic, as in silicosis, a careful building up of the work history of the patient, from the time he left school to earn his living, may be the only key that will unlock a diagnostic puzzle.

I would also like to point out that the clinical picture of silicosis among negroes is not the same as among whites. The negro is not as resistant to silica dust, he becomes tuberculous more readily and he succumbs more quickly. Where the silica dust exposure has been very severe, the clinical picture among negroes may approach the acute in type whereas among white men, working on the same job, it will be characteristically chronic.

An important phase of the silicosis problem is the incidence of tuberculous infection among the families of silicotics. In the early literature, especially that relating to the mining industry, the widow who had buried several husbands with miner's consumption was much in evidence. From this arose the general belief that there was not much spread of infection from silicotics with tuberculosis to their families. Undoubtedly, the situation varies locally and is influenced by race, general hygienic conditions and the severity of the hazard.

As a rule, the silicotic does not live long after his tuberculosis becomes open. Cummings of Saranac, in a study made in the Picher, Oklahoma District (unpublished) found evidence of tubercle infection in over 50 per cent of the children under 16 living in contact with silicotic patients having a positive sputum, but the infection was entirely of the primary type and there was no progressive adult tuberculosis. The whole subject of infection needs further study. We do not know what is the nature of the affinity between silica and the tubercle bacillus.

It is, unfortunately, a characteristic of silicosis that it tends to progress even when there is no longer an exposure to silica dust. The workman with a considerable degree of silicosis has an unfavorable prognosis even though he is removed from further dust exposure. He will probably succumb to tuberculosis. Where the damage to the lungs is slight, or moderate, he may go on for many years with little or no disability, but the overall mortality from respiratory diseases, particularly tuberculosis, among the silica dusty trades bears ample witness to the harmfulness that lies inherent in exposure to silica.

One of the difficulties that is constantly present in dealing with individual cases of silicosis is the estimation of the degree of disability. We would expect this in any chronic disease. The roentgen-ray film is not a satisfactory criterion. There may be evidence of a considerable amount of pathologic change in the film and yet the patient may look fairly well and be conscious of little impairment of his working ability. Chest expansion gives us no clue and little can be estimated from the patient's statements concerning dyspnea except in the advanced cases. Furthermore, it is not always possible to be certain of the presence or absence of infection—either from the symptoms or the roentgen-ray film. As a result, there has been a definite tendency to award compensation or other benefits on the basis of

a diagnosis rather than on actual disability—a most unsatisfactory condition of affairs. Some promising research has been started for the purpose of estimating impairment of pulmonary function without as yet producing results that can be converted into procedures for the clinician.

To sum up, silicosis is a widespread disease and is responsible for much tuberculosis among wage-earners. Its detection and control depend upon the accuracy and timeliness of diagnosis. As with other phases of the public health, successful achievement rests with the physician.

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DIABETES TODAY AND TOMORROW *

By Elliott P. Joslin, M.D., F.A.C.P., *Boston, Massachusetts*

The Hagedorn Era. Today we are standing on the threshold of a new era in diabetes. The Banting Era which we are now leaving was wonderful, and, even more, it was awe-inspiring. During these last 14 years you and I have seen diabetics gain hope, food, strength; insulin has breathed life into their dry bones and they stand upon their feet, a mighty army. Yet complications, although lessened in number and severity, persist and—I almost blush to admit it—diabetic coma is allowed to prowl about and decimate our diabetics by seizing the innocent, because undiagnosed, the ignorant and the careless. Therefore we have good reason to welcome the discovery of protamine insulin. The results with it in the hands of others and with my own patients are so distinctive that for me they amply suffice to name the new era in diabetes after its discoverer—the Hagedorn Era.

It is not so much that with protamine insulin the blood sugar of the diabetic can be kept normal for the 24 hours, as it is that along with a normal blood sugar we can infer that there will be glycogen in the liver and muscles, a normal content of fat in the blood and freedom from acidosis; in short, a far more nearly normal bodily mechanism is made available for the diabetic. But in a broader sense Dr. Hagedorn's discovery is noteworthy. He has made treatment with insulin safer and simpler and in so doing will multiply its use by practitioners and patients with consequent reduction in the complications and mortality of the disease. Protamine insulin cannot help raising the standard of diabetic treatment throughout the world. His discovery already is stimulating other discoveries in the technic of manufacture and administration of insulin. The old insulin was so good that we were too satisfied with it. There was too much of a *noli me tangere* idea about it. That conception has now been broken by Dr. Hagedorn and there will be a greater freedom in the world for various improvements in insulin medication. Finally, and perhaps best of all, he has demonstrated so plainly that all can read its force that what we need most in medicine today is not more beds for our patients, but more brains for their better care.

Not such a very great deal is yet known about protamine insulin. There are the two articles from the Steno Memorial Hospital in Copenhagen and the George F. Baker Clinic in Boston, in the January 18 number of the *Journal of the American Medical Association,* a monograph by Krarup, one of Hagedorn's pupils, and I have been privileged to see another. This is to appear eventually in the *Journal of the American Medical Association,* and in it Hansen, another of Hagedorn's assistants, shows that with protamine

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insulin the large livers of diabetics will decrease in size. Consequently I will recount briefly our experience at the George F. Baker Clinic and supplement it with information I have gathered elsewhere.

Professor Charles H. Best of Toronto showed my patients a week ago today various lantern slides illustrating the effects of ordinary insulin and protamine insulin when given to depancreatized dogs. With one dose of ordinary insulin the dog excreted 25 grams of glucose in 24 hours, but with one dose of protamine insulin the amount excreted was 1 gram. In the one instance the blood sugar after eight hours began to rise to high levels, in the other it remained practically normal for the 24 hour period. I will show two slides, already published by our group in the *Journal of the American Medical Association,* which illustrate the comparison between the short and prolonged action of a single dose of insulin and protamine insulin when given to a normal individual and the treatment of a diabetic by the two methods with the abolition of peaks and valleys and the flattening of the blood sugar curves. (These and various other slides were demonstrated.) They illustrate by blood sugar curves (1) the high morning fasting blood sugar which so often characterizes the patient treated with old insulin and the normal rising blood sugar if treated by the protamine insulin; (2) the reduction of the blood sugar using one dose of old in the morning and new insulin at night; (3) the use of protamine insulin entirely; (4) the reduction of four doses of old insulin to two of the new and of two doses to one.

Eighty of our patients have been treated with protamine insulin since July 1935. Insulin for about one-fourth of these has been furnished us by Dr. Hagedorn and the remainder by the Eli Lilly Company. The action of the two has been similar. We have treated young and old, mild and severe cases, some of short, many of long duration, complicated and uncomplicated, including surgical, obstetrical, those with normal and those with high blood pressure and cases with infections. There have been no allergic reactions. Dr. Long this morning told me there had been one marked allergic reaction proved to be due to the protamine in one of his cases. There have been no abscesses despite the patients mixing the protamine with the insulin in their own homes. Reactions have occurred and recently we have observed more than at first because we have taken more liberties with the protamine insulin. I think only once has glucose been given intravenously for a reaction, but we have given up to about 50 grams by mouth. Reactions have appeared more than 14 hours after a dose and several times with children before the morning insulin. Reactions are less apt to occur with a correspondingly low blood sugar with protamine insulin than with regular insulin. Usually the reactions have been mild and with warning, but occasionally they have been quite severe and prolonged. The reason for this has been that we have used more insulin than necessary in an attempt to gain quick control of the glycosuria. To transfer from old to new insulin in a patient taking four doses requires from a week to ten days. At first one is often discouraged. As a rule we have used, as did

Hagedorn, old insulin before breakfast and new insulin before the evening meal, but of late more and more we have turned to new insulin morning and night. Hagedorn used a diet of carbohydrate 110, protein 73, fat 161 grams, with a large proportion of it at breakfast. We have used the more usual American diet of carbohydrate 150 to 175, protein 75, and fat 100 grams, and occasionally more carbohydrate, but it is possible that it would be wiser to keep at 150 grams carbohydrate, particularly as it is probable that with protamine insulin lipemia and large livers can be avoided.

Protamine is easily obtained for the new insulin. At first it was supposed that after the protamine was mixed with the insulin, the mixture would keep for only one or two days. We have found it effective after 14 days and Professor Best told me it remained stable, if placed in an ice chest, for a month, or, in other words, after making the mixture the contents of the bottle would be used up before it deteriorated. Professor Best also told me it was desirable to wait for 24 hours after mixing the insulin and protamine before administration to the patient. The vial should be shaken before withdrawing the mixture, and in cleaning the syringe, if alcohol is used for sterilization, the syringe should be allowed to dry before inserting it into the vial.

I believe many advances can be made in adjustments of diets and dosages of the old and new insulin to the needs of the patients. In our clinic we are concentrating again upon blood sugar tests, five daily, to determine how we can improve our methods and establish rules of procedure. I shall take pains at the meeting of the American Medical Association in Kansas City to arrange that one of the booths in the Diabetic Exhibit shall be devoted to protamine insulin and shall secure for it charts and ideas from several clinics and arrange that many different clinicians describe their experiences with it and the methods they have found most useful.

No patient who has begun the new insulin has asked to be returned to the old variety.*

One mother says, "Dr. Joslin, we had not had a real night's sleep since Ruthie had that bad reaction eight years ago, but now we sleep all night without a thought of Ruthie, and even in another room. She has had protamine insulin five months. You have no idea what it means to us. I would love to have you tell everybody."

And now I will take up certain features characteristic of diabetes of today.

Diabetes Is a Life-Long Disease. I like to think of it as having begun with the tiniest baby in his bassinet and ending only with the last breath of life of the old man or woman. To be sure, we do not recognize the future diabetic in the nursery, and it is only in the last few months that I have realized that this also holds for the latter end of life. Indeed, only 63 per cent of my recent patients in Massachusetts when they died were classi-

* July 16, 1936. Correction of proof allows me to report that two of my patients have asked to be returned to the old insulin.

fied as diabetics. It is true 13 per cent had the word diabetes on the certificate, but escaped enumeration because other diseases took preference. Of the remainder who did not have the word diabetes on the certificate, 13 per cent would have been classified as diabetics if it had been placed there, but the remaining 11 per cent would not have been so classified. I object! At least our diabetics should have the recognition of dying *with* the disease, even all the more if they do not die *of* it.

Heredity. Diabetes is an out and out hereditary disease. The individual who is to have it is born with it. To a considerable extent it is our fault that we do not appreciate the possibility of a baby developing the disease, and this is, first, because we have not studied sufficiently its family heredity; and second, because as yet you and I have not been bright enough to invent methods which will show the congenital tendency to the disease. We want to be able " to look into the seeds of time and say which grain will grow and which will not," which child will eventually become a diabetic, and which will be guaranteed to be free from the disease. That is a pretty *arbeit* for us all to work out. Someone discovered blood groupings. Why should not somebody discover a method by which the seeds of diabetes can be detected? Himsworth has recently made a praiseworthy attempt to solve it, although his conclusions that it is the result of a relatively low carbohydrate high fat diet I consider erroneous, first because he assumes that one can argue from mortality statistics to incidence statistics and second because he leaves out of account the all important age-of-onset factor and its relation to the age of the population.

I will show the slide which, to me, is the most convincing of the data assembled by Priscilla White as evidence of heredity of diabetes. Upon it you will note the incidence of the disease in the control population and in the diabetic population. But, most of all, I would point out the incidence in dissimilar twins contrasted with the overwhelmingly high incidence of diabetes in similar twins.

TABLE I

The Incidence of Diabetes in the Siblings of (1) Non-Diabetics, (2) Diabetics, (*a*) Dissimilar Twins and (*b*) Similar Twins

Type of population	Siblings number	Per cent diabetic
1. Non-diabetics	682	0.6
2. Diabetics	2385	5.0
a. Dissimilar twins	16	12.0
b. Similar twins	13	70.0

Age of Onset of Diabetes. If we can assume that children are born with a tendency to the disease, when is it likely that the disease will become manifest? To this question we now have an answer, an almost uncanny answer, because of the similarity of onset by decades, no matter whether data are assembled in one clinic from time to time or in a group of clinics.

Suppose two diabetics marry and have a hundred children. These hundred children are fore-ordained and predestined to develop their diabetes according to a definite percentage for each decade from youth to extreme old age. Not all of the hundred will live to develop the disease, because many, as a matter of fact slightly more than half—56 per cent—will succumb to other causes, but the data are so definite that we can look ahead and form an idea of what percentage of these children will appear in each 10 years. This is shown in table 2.

TABLE II

Age of Onset of Diabetes—9853 Cases. Male 4639. Female 5214

Decade	Per cent appearing in each decade	
	Males	Females
1	4.96	4.45
2	7.24	6.27
3	9.57	6.08
4	13.75	10.84
5	23.32	22.96
6	24.19	30.25
7	13.65	15.76
8	3.23	3.14
9	0.09	0.15
Totals	100.00	100.00

You will notice from the table based on the onset of diabetes that 5 per cent of the number will appear in the first decade; that the increase is slight in the second; incidentally, there is a definite rise at puberty; that the percentage doubles in the third; again doubles in the course of the fourth and fifth, rising in the sixth to a peak of 24 per cent for males and 30 per cent for females and then falls off rapidly in the seventh; and by the eighth is even less frequent than in the first. By the ninth it is so low there is practical immunity.

In any consideration of diabetes today, we must appreciate the ages at which diabetes is liable to break out and therefore concentrate our measures to prevent and diagnose it at such periods. I hope you notice the decade at which there is a change in the tide of susceptibility to diabetes, namely that the onset of the disease begins to fall in the seventh decade. Actually the peak is in the sixth decade and at about 55 years. This is very important for us all to bear in mind. If we did not do so, with the rising mortality from diabetes as years go on, we might be confused, just as the public is perplexed and does not understand that the number of cases of the disease is bound to increase until the average age at death of everybody has risen from its present level of 48.7 years (1930) to 55 years. The onset of diabetes in these later decades is not rising and the reason for the high mortality is that younger diabetics have ceased to die and have swelled the mortality for later years.

Duration of Diabetes. Diabetes is a life-long disease, because it begins at birth and lasts until death, even though it may be unrecognized at either end of life. But it is also deserving this terminology, because when it becomes manifest, it lasts so long. For this statement I have good proof. Thus, of my 300 glycosuric doctors, the average duration of the disease among the 96 true diabetics who are dead was 11 years, and already among the 155 true diabetics living has reached more than 10 years, and I am sure that in this group there are many who have no intention of laying down their stethoscopes until they have lived out their full length of life. Indeed, of the fatal diabetics, my average diabetic doctor's age at death, 1929 to 1936, was 68.5 years as compared with non-diabetic doctors, 63 years, whereas among my living diabetic doctors the average age is now only 55 years. Think of what these doctors do after they develop diabetes. Who played a leading part in the discovery of pernicious anemia and received a Nobel prize?

My medal diabetics attest the long duration of the disease. Already there are at least 400 of these who have lived longer with the disease than was their lot according to insurance life expectancy tables. The average duration of 981 of my diabetics, who succumbed in the last five years, was 11 years, and as I contemplate the living patients, and especially the living children of whom there are in our group 188 whose diabetic life is over 10 years and of whom at least 53 have lived over 15 years since the onset of their diabetes in their childhood, I am sure that the average individual who develops the disease in 1936 or thereafter, will round out 20 years. For your encouragement, also, I will add that 10 times as many of my fatal cases in the last few years lived over 20 years as prior to 20 years ago. Finally, before 1914 the average age at death of my cases was 44 years, and now like the doctors, it is 63 years.

At the present moment the changing duration of diabetes is forced upon me in another way. In tracing the condition of patients with onset of diabetes under 40 years of age I find it extremely more expensive and time-consuming than hitherto because these patients live so long. When my cases died with an average duration of 5 years it was a simple matter to learn their whereabouts, but now it is extremely difficult, particularly in the case of the females, because they change their names. I suspect in a few years that it will be almost impossible to trace patients, as I have done hitherto, simply because they live so long.

Dr. Philip B. Matz of the Veterans Administration tells me that of 1243 living cases the average age at time of onset of the disease is 32.9 years and already the average duration is 9.1 years. There should be little difficulty in tracing the veterans, and they may furnish us ultimately with our most reliable diabetic statistics.

For the doctors this life-long duration of the diabetic carries a lesson. Doctors practice only about 30 years. When a doctor sees a diabetic patient, unless the doctor is very young, like most of you, the chances are that

his diabetics will outlive him. Here is a two-fold lesson. First of all, learn all you can from each diabetic so that you yourself can profit from the experiences which he goes through, and in the second place, remember that if you want a diabetic for your medical life, you must keep him alive. But, how are you going to do it? The only way that anyone can keep a diabetic under observation over a period of years is to study more than the diabetic studies; to be able always to tell him something which he does not know and has not seen in the newspapers; to learn so much about the disease that you can detect his errors; to combine, either in yourself or those associated with you, every particle of knowledge which a student, a social worker, a dietitian, or a nurse has, so that you can help him, and then either teach him yourself or get these friends of yours to have that pleasure. To hold the patient you must be in touch with students and investigators or else be a student and investigator yourself, because otherwise your mind will not be open to the truth and profit by it. If your diabetic wanders to someone else, it is almost invariably your own fault if he does not come back to you. Diabetes is a life-long disease, and to treat it one must approach it from that point of view. The diabetic expects the advice and care which will protect him his entire life.

I count upon diabetes lasting as long as 20 years on the average, because I know you will learn control of the disease. How will you do it? For a discussion of this question I now ask your attention.

Control of Diabetes. First of all, we all would like to go further and prevent it. That is more easily said than done because 25 per cent of the population in the United States, according to Priscilla White, are diabetic carriers. This does not mean that they will develop the disease, but they can transmit it if they marry an individual who is also a carrier. To me that vast number of carriers of diabetes, nearly 30,000,000, in our country, makes it preposterous to attempt to institute any extreme measures of prevention along eugenic lines. We can teach one diabetic not to marry another diabetic. We can talk about one diabetic family not marrying into another diabetic family, and all that is useful. However, we must remember that of our 100 children, born of two diabetic parents, only 56 will live long enough to develop the disease, and that if but one parent has the disease and the other is simply a carrier, the number of actual diabetics falls very rapidly. Indeed, if two diabetic carriers marry, the per cent of their children who actually will come down with the disease is only ½ the expectation of 25—12.5 per cent. Of course, this is not an inconsiderable number, but it is very different from saying that 100 per cent of the children will develop the disease.

Furthermore, suppose that a few should develop the disease in the latter years of life. At that period we know it is quite amenable to control and the disease is not so terrible after all. Of course, I firmly believe that more bright men than fools are diabetic, and that there is enough of a pituitary element in the disease to make the diabetic outstanding in brains, as well as

in stature and precocious development. I do not approve of two diabetics marrying and having children, but I will not go so far as to say that a diabetic should not marry a non-diabetic in a non-diabetic family and not have children.

Heredity is important from another standpoint. If we know there is a diabetic heredity in a family, we can seek to prevent those influences which are well recognized as favoring the onset of diabetes in that family. The danger of obesity can be preached to parents and children and when we do that we are standing on sure ground because in the adult, obesity is a forerunner of the disease in an extraordinarily high percentage of the cases. A good muscular development can be favored on the ground that, from experience with diabetic patients, we know without exercise the treatment of the disease is difficult. I will not say that we should make suggestions about the quality of the diet. It is safer to restrict the quantity. Himsworth would have us believe a high fat-low carbohydrate diet would predispose to diabetes. Rabinowitch, from newspaper reports, appears to have found no diabetics among Esquimaux.

Simpler Diagnostic Methods. Easier methods in securing a diagnosis of diabetes should be adopted. The most annoying group of glycosurics, as I have often said, is the group in which the diagnosis has not been cleared. My group of this type is particularly large because it goes back before the days of routine blood sugar tests. Even now it is too large, because so often patients do not want to come back for a glucose tolerance test. In desperation a few weeks ago I decided to clear up as many patients as possible during the first visit. For this purpose, I have given them 50 grams of glucose. I tell them frankly that unless the test of the blood is positive in an hour one cannot draw conclusions from it. But it was a satisfaction in one week to settle the diagnoses of four borderline cases in this manner, and I suspect that I shall follow up this principle still more. Incidentally, think of the saving of costs to the patient and of work to the laboratory.

Costs of Treatment. Costs of treatment of diabetes constitute an important factor in the treatment of this disease which lasts for life. We must consider these costs very seriously from the patient's point of view and from the doctor's point of view. No patient should be deprived of treatment on account of the cost. In order to protect the physician, arrangements must be made by which blood sugar tests can be done very reasonably or without cost. We doctors in the hospital have a great advantage in this regard. I feel that some permanent arrangement must be made by which doctors in private practice will be accorded the same relative ease in obtaining blood sugar tests from indigent patients and low income patients as are afforded doctors who happen to have a position on the staff of a hospital.

Responsibility of Diabetics. Responsibility for their own careers must be assumed more and more by the diabetic of today. There are so many of them that unless they demonstrate that they can be independent, self-sus-

taining and make a success in life, a prejudice will arise against the whole group. I think diabetics are a superior race of individuals and therefore anything which can be done on their part to prove this and to show to all that they are not marching in a bonus parade to Washington is desirable. Each diabetic should hoe his own row.

Furthermore, each diabetic should make it his business in life to help another diabetic with encouragement, advice or financial assistance. Diabetics as a class are neither very rich nor very poor. Their interests are one Realizing this, " Every man should help his fellow."

Treatment: Diet. The dietetic treatment of diabetes is so generally agreed upon today that consideration of it can be dismissed in a few words. Few there are who do not give their patients carbohydrate between 100 and 200 grams, protein between 60 and 90 grams, and fat enough in calories to enable the patient to maintain a weight which is normal or, in older patients, a trifle below the normal standard. It is not the details of diet and calories that are important, but rather the details of teaching the patient how to use the diet and calories. There are all sorts of methods, and each doctor finds out for himself what is most applicable to his own patients. Book knowledge will not do alone for these patients, they must be taught by illustration. They often learn most from one another. The class method of instruction is of enormous advantage. When I demonstrated to the class the reduction in the Benedict test which followed the use of four drops of the juice of one grape, I did more good than if I had talked about the dangers of eating grapes for an hour. Incidentally, after I did remove four drops of juice from the grape, the grape looked just as large as it did before, and that also impressed the class. I will pass over the diet, because I am sure it would be too much " coals to Newcastle " to speak of it here.

Exercise. Exercise should be utilized even more than it is. I would like to show you certain slides which represent experiments conducted by my colleague, Alexander Marble.* All of these slides portray curves which show the effects of exercise as compared with rest with or without insulin fasting before breakfast. The secret lies in insulin. The normal individual and the mild diabetic have insulin, but the severe diabetic must buy it if he wishes to be benefited by exercise. Last year we gave our children insulin between 45 minutes and an hour before breakfast, and the children played more or less after it and thus brought their blood sugars down to a reasonable level before they started to eat.

Camps. Our diabetic camps, the last two years, have taught us a great deal about the management of diabetes in children and suggested much which I am sure we can utilize with adults. We were able to keep a child at camp at approximately one-half to one-third of the cost that child would need if he stayed in the hospital. In these various camps we built laboratories, costing from $200 to $700, and we were able there to carry on the

* The paper has been accepted for publication in the *Archives of Internal Medicine.*

treatment of the diabetic children more efficiently and more efficaciously than in the hospital. We had them all day in both places, but we could provide recreation, could supervise their diets more accurately, and give them more pleasure in the camps.

A Diabetic Boarding School. The lesson we learned from the summer camps was that with our diminishing resources we must provide for the care of the diabetic children at other times of the year in similar fashion. This has led to the establishment of what I think is a new idea in the management of children, namely, a Diabetic Boarding School. For practical purposes this is what the Prendergast Preventorium amounts to so far as our diabetics are concerned. Originally at this Preventorium underprivileged children and undernourished children, but no children with tuberculosis, were taken. It is under the control of the Tuberculosis Society. Last year they agreed to take our children at $10 a week, and we now have 10 children there, and they are supervised by a nurse skilled in their care and under the general direction of Dr. Priscilla White. These children are furnished their education by the City of Boston. Their board is paid either by them individually, or by the Welfare Societies—public or private. We are trying to centralize there, not only all the children—there are not so many of them—who need help away from home, but also other children who cannot be well-cared for at home. During the summer we had between 30 and 40 boys at this camp, but in the winter we have both boys and girls. When one of the children became ill he instantly was moved to the Deaconess Hospital. Camps and boarding schools for the uncomplicated cases—hospitals for emergencies. And now I want an inexpensive boarding house home—convalescent home—convalescent hospital for my older patients!

Wandering Diabetic Nurse for Adults. Another idea has developed as a result of our work with children. Originally we employed the Wandering Diabetic Nurse only with our children and indeed Miss Winterbottom still acts as a Wandering Diabetic Nurse for them, but we have found lately that the children are doing so well that they require less of her time. You can hardly guess the type of patient she is helping this winter in their homes. Instead of our youngest patients, she is instructing, teaching and caring for our oldest—the old children above the age of 60 and 70 and even 80 years. Such patients one hesitates to move away from their home environment into a hospital. We have found that her services to these old people are most valuable and of course the cost to the patient is greatly reduced. I commend to you both the idea of a Diabetic Boarding School and the use of a Wandering Diabetic Nurse.

What Is a Wandering Diabetic Nurse? She is a composite of a nurse, a dietitian and a social worker. Few institutions and still fewer outpatient departments and almost no doctors can enlist three separate individuals to care for their diabetics, but each diabetic needs the services represented by these three professions, and the services must not be rendered routinely, but they must be specialized. The individual who assumes the

task of helping in diet, in nursing and in the social adjustments of these patients must be trained and indeed a specialist in diabetic work. Therefore, it is essential to combine all in one and therefore I attach great importance in any undertaking for improvement in the treatment of diabetes to the position of Wandering Diabetic Nurse.

Let me illustrate a little more in detail the desirability and, indeed, necessity, for such an individual. At the New England Deaconess Hospital we have 1200 diabetic admissions a year, but there are few hospitals that have 100 and there are a great many hospitals in smaller communities that do not have 25. When one divides up the total number of patients throughout the year, there is not work enough for three separate individuals and no nurse, dietitian or social worker will acquire experience enough individually to care for these patients properly. If we can center our instruction in one individual, gradually the hospital can develop specialized treatment so that not only its own patients will receive instruction along these different lines, but the instruction will be so good that doctors in the community will wish to take advantage of the service as well. I believe the endowment of a Wandering Diabetic Nurse in a hospital with 100 beds would be of immense advantage to the community, because her services could be drawn upon by physicians within the hospital's area in addition to the work she did actually in the hospital. There she could serve, not only in connection with the care of the diabetic patients in the institution, but also, because of her wide experience, could aid in teaching nurses the treatment of diabetes.

Diabetic Coma. You and I know that it is very easy, even in a large hospital with hundreds of diabetics, to overlook cases of diabetic coma. We doctors overlook them. Nurses constantly overlook them and I regret to say that within the last 12 months we had one patient enter and die within 190 minutes of admission with diabetic coma. I am quite sure that such errors exist in other hospitals, and, in fact, I know and have personal cognizance of such errors. In our own case, experienced individuals were so absolutely positive that the patient had hypoglycemia that blood tests were delayed. I will say, however, that I really do not believe that the patient who died would have recovered, even if he had been treated for diabetic coma from the first minute he entered the institution. But my conscience would feel easier if he had been given every possible chance despite a blood sugar over 1000 milligrams, a CO_2 combining power of 2 volumes per cent and a blood pressure doubtfully obtained at 70.

Hospital Instruction. Training in a hospital is desirable for practically all diabetics, and especially for those with small means. Gradually we have reduced the length of stay in the hospital from 30 days, prior to the discovery of insulin, to about 7 days, and I judge even less if we exclude cases with gangrene or infections of the feet. A year or two ago I advocated weekend hospital treatments for diabetics and still approve of it. Repeatedly we have patients come in of a Friday or Saturday and go to work

of a Monday. Sometimes they enter for more than one weekend. With lessening available funds to help needy patients, we are shortening more and more our hospital stays. Of course one cannot complete the treatment of a case or expect to do much more than to inaugurate treatment, but this alone is of great advantage and the balance of the treatment can be supervised through a Wandering Diabetic Nurse or by office visits. To secure success from a short hospital stay, the instruction must be concentrated. One cannot give long talks to patients. Recently we again changed our methods and we doctors, individually, give one talk of 30 to 45 minutes each day. This is supplemented by short classes or desk instruction or bed-side instruction by the teaching diabetic nurse in the hospital. More and more, however, I think we are emphasizing the help which one patient can give another. Indeed, over and over again I hear from patients that they will follow treatment, because of the complications which they saw other patients had in hospitals as a result of neglect of treatment. One can tell a patient to follow treatment and keep his feet clean, but the effect produced is nothing compared with seeing a patient who has his leg cut off, because he has neglected his diabetes and carelessly cut a corn. Therefore, just as we have made our money go farther with children by sending them to camps or to a diabetic boarding school and bringing into the hospital only the emergency cases, so now we are more and more bringing into the hospital diabetic cases for short periods and thus are making it possible to double and treble the number of patients who will have an opportunity to learn how to care for their diabetes.

Decision in Surgical Advice. Diabetics, and doctors as well, are dilatory in their decisions. Against our better judgment we are influenced by protests of the patients and delay operations which are indicated. Last year all of us, surgeons and doctors, consented to postpone an operation on an old man because of the faintest possible chance that his foot might heal. It cost the hospital and family at least $600 and in the end, after months of considerable suffering, the operation was performed. For that same amount of money, 60 children could have had instruction and care of their diabetes and happiness for a week at a diabetic camp. When all the doctors and surgeons are unanimous in their opinion as to what is best to be done for the patient, the procedure should be carried out or the patient should be discharged to the treatment of another institution or doctor in whom he has more confidence.

Close Supervision of Diabetics. Diabetics require closer supervision. In an earlier portion of this paper I called attention to the fact that 10 times as many diabetics live 20 years, or more, now than they did prior to 1915. I did not add, however, that only one diabetic in eight of my last 900 to die, just prior to March 1935, reached this duration. It is perfectly possible, in my opinion, for diabetics on the average to live 20 or more years, but they will not do so by luck. If we want our diabetics to live, we must protect them from needless death, and these deaths today are primarily from

two causes, just as they have been for years past. First, deaths from coma and second, deaths from infection, chiefly of the lower extremities. There are other needless deaths which make so desirable a renewed effort to avoid them. Tuberculosis relatively is far greater among diabetics than in the general population. Thus Dr. Howard F. Root has shown that in Massachusetts it is more than 10 times as common in diabetic children as in the ordinary school child of similar age and two or three times as common in diabetics of all ages.

Cancer is steadily increasing and it is of great interest in this connection that cancer of the pancreas is four to five times as frequently observed among diabetics as among non-diabetics. This is a problem for continued study. My opinion upon cancer may be biased because of proximity to the Palmer branch of the New England Deaconess Hospital in which so many cancer cases are treated.

All are aware that coronary thrombosis and angina pectoris are conditions far more frequently observed in diabetics than in non-diabetics, but these are not so easily remedied by observation of the patient. They are subjects for research. On the other hand, coma, gangrene, osteomyelitis, tuberculosis and cancer are the complications which can be detected early and treated well. What is the significance of all this, therefore, in our consideration of diabetes today? In my opinion, we must change our method of treatment. Hitherto I have not asked patients to come back regularly for observation, but beginning January 1, 1936, I am telling each patient, specifically young and old, recent case and old case, that he should keep under the supervision of some doctor and be looked over as a routine at least every three months more or less, according to the case. I intend to give each patient, in the letter I send him after his visit or on a card, a statement that he should see some doctor at least within three months after his visit to me. Most doctors do not like to ask patients to come back for fear they will be accused of grasping for money. I know that many of us who see patients for other doctors hesitate to ask patients to come back or even to communicate with them, but I believe it is possible that a more aggressive attitude can be adopted and in doing so the family doctor as well as the patient can be protected. At least, I am willing to try an out and out experiment and risk the opprobrium which it may arouse.

Coma still causes more deaths in diabetes than it should. It is true that the mortality has fallen from 64 per cent (among 325 of my deaths) prior to May 31, 1914, to 6 per cent (among my 981 deaths) ending in March 1935. These figures apply to deaths both in and outside the hospital. By and large, however, throughout the country, I suspect that the mortality from coma is still between 10 and 20 per cent. How can this be remedied? In general by education of the patient and insistence upon his keeping in touch with his physician and always reporting immediately when any unusual symptoms occur. The opportunity for improvement does not rest alone with the patient and with the general practitioner. I

know from our own bitter experience that treatment in the hospital can improve. Cases of coma are still unrecognized or confused with other states. My colleague, Dr. Root, points out that errors in diagnosis are always to be expected in moribund patients, but he too feels, as I do, that this is no excuse for the delays which sometimes arise, and I fear far more frequently than is generally believed, before the diagnosis of diabetic coma is made after the patient reaches the hospital.

A Coma Drill. A coma drill in a hospital is essential, just as is a fire drill. Neglect to have one I think will surely result in unnecessary damage to the patient and the reputation of the hospital. It is easy enough to send a specimen of the blood to the technicians in the laboratory by day, but at midnight and in the early morning hours, when technicians are not available and house officers are out of practise in determination of blood sugars, CO_2 values and non-protein nitrogens, it is very easy indeed for mistakes in analysis to arise. I suggest for your consideration the establishment of a diabetic coma drill in your hospital with records to be kept as to how long it takes to secure blood and make a diagnosis. Minutes count in the treatment of diabetic coma or hypoglycemia and arrangements should be perfected, just as I am sure you already have arrangements perfected for the reception of a coma case into the wards.

Follow-Up of Discharged Cases. The sequel of the old man or woman whose toe or leg has been removed, because of diabetic infection or gangrene, has not been encouraging. I hesitate to state the few years which such patients live. My colleague, Dr. Root, has been much interested in this, particularly because of his association with Dr. McKittrick in compiling the monograph on "Diabetic Surgery." Recently Dr. Root has arranged that once a week the relatives of the patients with lesions of the legs should see him for a talk so that they could be prepared for the care of their parents, brother or sister, wife or husband, when discharged. This has proved to be quite worth while. The conference has taken place in the early evening when relatives visit the patients.

Dr. Root has also instituted another forward step in that the Wandering Diabetic Nurse sees the patients with a lesion of the lower extremities within 10 days after discharge. The follow-up of this special group of cases has also proved well worth while. As a rule, patients coming with lesions of the lower extremities are patients who are poor. They need supervision at home. We need more organization in their care.

Insulin. Insulin gave us a new diabetic to treat. Even now we hardly have begun to realize its benefits. I am sure they are far more than those represented by prolongation of life or reduction of complications. The spirit, as well as the body of the diabetic, has been protected. Today treatment with insulin is so well understood that it is almost automatic and if a doctor is really interested and will read his medical journals or even the standard textbooks, he will not go far astray. No longer do we try to give one large dose (I am speaking of regular insulin, not protamine insulin)

and expose the patients to reactions when two doses will be more efficacious. If three doses are needed, often the third can be taken conveniently on retiring so that an approach to a normal blood sugar can be secured on waking. We all know that insulin works and that if unusual dosage is necessary there is a reason for it and that it is for us to find the reason. Generally the reason lies in an infection, open or concealed. Often it is associated with other glandular trouble. Seldom it is the result of faulty administration, but quite commonly a sequence of a poorly-balanced diet and a previously neglected diabetes. Mrs. St. C. had a severe reaction when the site of her injection was changed. She is an insulin resistant case, taking 400 to 500 units. It is a wonderful step forward that now we realize that insulin will act favorably upon the standard case of diabetes.

None of us are unmindful of errors with insulin, in measuring dosage, in methods of administration, reduced efficiency because of insulin lumps and of the atrophies occasionally developing without known cause. Most of all, however, the dangers of hypoglycemia have been foremost in our thoughts. These have been greater of late than formerly because today with insulin the diabetic is so well that he wanders farther afield and so is under less close supervision.

The Rôle of the Liver and the Interrelation of the Ductless Glands in Diabetes. The liver and the ductless glands are bee hives of experimental activity in diabetes today. That the excessive deposition of fat in the liver can be prevented by choline is a triumph attained by Best and his co-workers in Toronto. The next speaker, Dr. C. N. H. Long, will tell you of the diabetic wonders achieved by the experiments of Houssay upon the pituitary and the new operations involving not only the pituitary, but also the medulla and cortex of the adrenal, which he, in association with his colleague, Francis Lukens, has devised, executed and interpreted. Indeed, Dr. Long's paper will give you a far better idea than mine of what to expect in the Diabetes of Tomorrow.

CLINICAL ASPECTS OF CIRCULATORY DYNAMICS IN ARTERIAL HYPERTENSION *

By Arthur R. Elliott, M.D., LL.D., F.A.C.P., *Chicago, Illinois*

We know that of patients who have persistent high blood pressure a considerable percentage—estimated by some authorities to be as high as 25 per cent—will die of causes that have no bearing whatsoever on their hypertension. The remainder will succumb through development of some condition directly attributable to the prolonged circulatory strain. A small percentage will die of progressive renal insufficiency, resulting from arteriolar changes in the kidney or more likely from progression of an unrecognized obscure nephritis. A larger number will develop cerebral accidents, the so-called hypertensive encephalopathies. The remainder, predominantly the largest group of hypertension casualties, die of cardiac failure. It is with this latter aspect of the ultimate consequences of arterial hypertension that the present discussion is concerned.

Certain facts or inferences emerge from practical experience with the run of cases of high blood pressure. For example it would appear that patients who have a marked hereditary bias toward vascular pathology usually sustain the strain of elevated pressure for longer periods than those without such a background. This is difficult to explain unless it be that certain constitutional resistances enter into their tissue make-up as provision against this inherited liability, and so insure their survival, or perhaps it may be because these individuals develop high pressure earlier in life and more gradually than do others. Another observation common to all experience is that high blood pressure developed in association with or in consequence of certain other disorders may be viewed more tolerantly than when it emerges as a single symptom. For example when it exists in common with diabetes, hyperthyroidism, chronic anemia, uterine fibroids, prostatism, etc., it rarely is as malignant in its effects, and moreover tends to share in the beneficial influence of therapeutic control of its associate. In passing it should be noted that exactly the opposite is true when hypertension results from nephritis. Another well-tolerated form of hypertension is the elevated systolic pressure resulting as a compensatory response in aortic atherosclerosis. This is compatible with long life and reasonable efficiency. I get the impression from a review of my experience that what has been called the neurogenic variety of hypertension has a milder prognosis although usually a more stormy symptomatic course than is true of other forms. The blood pressure in such instances is particularly unstable, being subject to wide fluctuations, so that there is more easement to the cardiac and vascular strain than is available in other cases. These are the

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patients who derive the greatest benefit from appropriate personal hygiene and especially from bed-rest and hospitalization. Other things being equal it is a fact that marked decline in average pressures induced by rest either alone or combined with simple sedative medication foretells a better prognosis. To complete these brief notes on prognosis in arterial hypertension I should revert to the well known fact that the outlook is in all ways more favorable among women than men. They live longer and a higher percentage of them die of causes not connected with their hypertension. This strange fact is not because women do not have pressures as high as those of men. Its significance may lie in some resistance-provision in the female circulatory structures inherent in their biology as a survival factor or in the less strenuous life of the average woman as compared with the average man. Moreover another factor may enter in and that is the influence of the menopause which slows down many women and may thereby prove a buffer mechanism.

This brief reference to certain considerations having bearing on the prognostics of hypertension yields the impression that incidental factors and influences that tend to moderate the persistency and severity of the strain prolong the ability of the heart and vessels to carry the load and that the heart is preponderantly the determinant of the prognosis. The mechanicopathology of the heart and how it comes about is therefore the great concern and interest in the clinical study of blood pressure.

I need not labor the point that patients coming under observation for the first time with very high pressures and evidences of strain in the cardiovascular apparatus may survive for years even in the face of conditions that appear absolutely to preclude such a prospect. This fact stands as a tribute to the extraordinary capacity of the heart to tolerate profound maladjustments in the dynamics of the circulation. About the only thing, generally speaking, that appears to interfere with this compromise is the presence of coronary artery disease, especially coronary occlusion with infarction of the myocardium, but in exceptional cases even this development may not prove an intolerable handicap.

The work of the heart depends not only on the peripheral resistance but also upon the amount of blood its chambers discharge. Cardiac output has been the subject of study by several investigators but for various reasons no uniformity of opinion as to the reliability of the results secured has been reached. For what they are worth the significance of data accumulated in arterial hypertension appears to prove that basal cardiac output remains unaltered so long as congestive heart failure has not supervened. The findings, imperfect as they may be, yield the general impression that the high pressures of chronic hypertension are neither established nor maintained by an increase in the volume of blood discharged by the ventricle. These findings rather support the conclusion that the exaggerated pressures and consequent increase in heart work are due to increased peripheral resistance re-

sulting from precapillary constriction which is the characteristic feature of hypertension.

Inasmuch as the work done by the heart pump is almost entirely spent in overcoming resistance, the fall of pressure from aorta to periphery being extreme, it follows inevitably that the capacity of the ventricle to maintain efficiency in the face of permanent and steadily increasing resistance must in time become exhausted. That this event is so long postponed may be because coronary blood flow is chiefly dependent on aortic pressure, any increase of which results in freer flushing of the myocardium. This is a matter of pressure rather than of cardiac output or heart rate which influence the coronary circulation far less. An added beneficial effect on myocardial nutrition may result from the fuller clearance of the vascular stream bed resulting from the slow heart rate and prolonged diastole present during much of the clinical course. As an offset to this advantage stands the undoubted fact that the coronary arteries are in some manner detrimentally affected by continuous increase in blood pressures so that coronary obstruction develops more frequently in these subjects than in any others.

The ultimate effect upon the coronary vessels even without the dramatic event of occlusion is to produce in the majority of cases varying degrees of narrowing of their caliber from sclerosis, often with secondary fibrotic alterations in the muscle fibers throughout a considerable area of the heart wall. That these scarrings are not more frequently detected is perhaps because the gross-pathologist is apt to confine his inspection of the myocardium to a search for infarctions and overlooks less obvious defects. This point has been emphasized by some pathologists, notably by Klotz. The matter is important because we are gradually swinging around to the position that it is not work exhaustion per se that causes the hypertensive heart to fail but interference with the chemical exchanges in the myocardium through progressive restriction of the coronary blood supply. Lowering of the systemic blood pressure cannot necessarily be taken as evidence for or against the existence of widespread coronary disease. There exists no constant ratio as between height of blood pressure and myocardial dysfunction. It is not exceptional to see blood pressure maintained at or near its usual level after coronary occlusion, and many patients retain heightened pressures despite extreme degrees of myocardial failure even up to death itself. It was emphasized years ago by Norris that the last ounce of reserve power of the heart may be put forth in maintaining blood pressure levels and the heart muscle be actually at the point of final failure notwithstanding a pressure well above normal. It is a mistake then to expect necessarily a fall in blood pressure with cardiac failure no matter how induced. This may be because pressures are much more easily influenced by changes in the caliber of the peripheral arterioles than by alterations in cardiac output, and peripheral constriction may be at such a high point that even a small output may suffice to maintain pressures at an abnormal level.

In our zeal to interpret the importance of the heart and the larger vessels of the distributing system it should not be forgotten that these more obvious phenomena are but means to the end that an adequate capillary flow be constantly maintained. This is a point much neglected and yet the picture is not complete if we do not take into account what goes on in the vascular channel distal to the heart and aorta. It is well to remind ourselves that the dynamics of the circulation are not entirely a function of the heart pump. The initial propulsion of the blood appears to be its sole and only function; in short, as Harrington Sainsbury puts it, the heart is a "power chamber." After the cardiac systole is completed diffusion of the blood throughout the circulatory tree becomes the business of the arteries. Inasmuch as systole is shorter in time than diastole it might appear that the arteries absorb a larger share of the work of circulatory movement than does the heart. If there be truth in this assumption then what goes on in the arteries in hypertension becomes of great importance to the fate of these patients. First of all it is well known that the aorta is essentially an elastic tube cunningly devised to receive the oncoming blood from the heart with, as it were, "open arms." After distention follows recoil, allowing the "run off" into the smaller vessels to continue during diastole. These lesser vessels possess little elasticity and though heavily endowed with muscular equipment they have little propulsive power. They are but smooth channels allowing flow without friction or loss of head until the precapillary bed is reached where the stream slows down and pressure sharply declines. There is comparatively small reservoir capacity in the arteries. Such as there is depends on their elastic stretch and this, except in the aorta, is not considerable. Their maximum extensibility lies slightly above the usual systolic pressure in health. Above that limit the cubic enlargement of the arteries is less and less as pressure rises and the heart responds to its increasing labors. It is a mistake to assume that the compensatory hypermyotrophy that thickens and strengthens the heart wall does not affect the arteries in like manner. This is shown in cross sections of these vessels and to the palpating finger they seem rigid and taut. This compensatory reënforcement by the arteries offers a valuable element of collaboration to the heart in carrying on its task in the face of increasing resistance. How important this ancillary action may be is revealed in due time. The unfortunate predicament of the arteries in this circumstance is to be caught between the upper and nether millstones —the strongly acting hypertrophied heart on the one hand and the constricted precapillary bed on the other. During the sthenic or fully compensated stage of hypertension the arteries are observed to be taut or rigid but they are not tortuous. Under the excitant effect of persistent internal overpressure molecular degenerative changes in the vessel walls result and progress until what Norris has designated a "break in vascular compensation" supervenes. This is revealed by a rather rapidly developed tortuosity and relaxation of accessible arteries. We may palpate it best in the brachial and femoral arteries and see it strikingly in the retinal field. The

effect of this relaxation of general arterial tone upon the heart proves unfortunate because thereby is shifted upon that already overworked organ an added burden. For years I have watchfully observed this sequence of arterial events and find reason to regard it as extremely significant. The advent of arterial dilatation often proves to be a forerunner to the development of weakness and failure of the ventricle with the phenomenon of congestive heart failure.

Another arterial phenomenon that will profitably repay study in hypertension is the pulse rate. During the greater part of the clinical course the pulse rate is not increased, indeed it is often slower than normal. In experimental work it has been found that when the heart rate is slowed not only is the blood given a longer time in which to pass the peripheral narrows but the longer diastole allows a more complete filling of the ventricle during its relaxation, thus offsetting the effect of slow rate on cardiac output. Another consideration that may render the slow heart rate of decided benefit is the theoretical deduction based on the known laws of oxygen diffusion that the enlarged heart with its thickened muscle should require a longer time between beats to recover than does the normal sized organ. Since there is no acceleration of rate in most instances of hypertension and little evidence exists of increased stroke volume, an increased minute flow might be assumed. Many workers employing various methods have studied this phase and failed to demonstrate any increase in minute volume flow—indeed it may even be below normal limits. Leaving aside physiologic explanations, which as yet appear to be in a confused state, the clinical fact stands out clearly that a slow pulse rate in hypertension is the best assurance we have of adequate reserve on the part of the heart pump. With increase in heart rate, which in time becomes inevitable, abbreviation of diastole diminishes the inflow quantity of blood thus reducing the amount of blood ejected during systole. Not only does the general circulation decline in proportion to this handicap but, still more important to the patient, the coronary circulation is detrimentally affected by decline in aortic outflow. The thickened muscle fiber of the heart is a decided asset in overcoming arterial resistance but at the same time it suffers from a chemical disadvantage—any decline in coronary flow laying it open to the accumulation of oxygen lack which the myocardium is much less tolerant of than is skeletal muscle. In this manner there comes about with the advent of rapid heart rate a vicious circle tending eventually to produce congestive failure with its train of disadvantages.

Some controversy has existed as to whether the systolic or the diastolic pressure constitutes the breaking strain upon the ventricle. Determination of the time course of the pressure curve in the ventricle shows that no blood is expelled until the maximum tension is developed. During the expulsion of blood into the aorta the pressure in the ventricle remains nearly constant, the curve showing a flat top. This would go to show that the greater part of the work done by the heart muscle is expended in raising the pressure of the blood to the diastolic level and would give that factor the greater im-

portance. This seems to be in keeping with clinical experience, for we know that a continuously high diastolic pressure is not well tolerated although per contra a very high systolic pressure may be carried for years without evidence of cardiac exhaustion provided the diastolic pressure remain low. This gives the pulse pressure significance merely as a rough index of the mass movement of the blood without any fixed prognostic importance. During the stage of adequate compensation the circulation to all appearances is carried on normally. In the main the elevated systolic pressure may be considered as evidence of relatively normal heart power and normal blood flow. Yet we must not assume that volume flow runs proportional to blood pressure, for the factor of peripheral resistance must be taken into account. Neither is it, as already pointed out, correct to infer that an abnormally high blood pressure constitutes an indication of adequate cardiac power. Even with the signs of congestive failure present throughout the body blood pressure may still remain considerably above normal. Indeed it may be said that there are no definite rules whereby we are altogether safe in judging the import of either a rise or fall of blood pressure. In patients seriously embarrassed a rise of pressure may denote restoration of compensation and general improvement, whereas with certain others it may prove unfavorable, implying the advent of uremia. On the other hand a fall in pressure levels may prove a favorable indication, signifying lessened toxemia and diminished peripheral constriction. Heightened pressure is consequently not necessarily an index of good cardiac response nor is a lowering pressure portentious of approaching cardiac exhaustion. The claim that arterial hypertension is a conservative mechanism rendered necessary to maintain an effective working of the organs, especially of the kidneys, does not receive striking confirmation from clinical observation, for many patients appear to profit greatly and suffer no decline in renal elimination when a high blood pressure is lowered by effective treatment. To place implicit trust in instrumental readings as an index of progress or for prognosis in any given case is to invite error. The patient's general condition and evidence of well-being, his range of efficiency, the presence or absence of well attested signs of circulatory embarrassment constitute better grounds on which to form a judgment than information procurable from blood pressure figures alone with theoretical deductions therefrom.

DEXTROCARDIA IN CHILDREN *

By Henry A. Reisman, M.D., F.A.C.P., *Jamaica, N. Y.*

The term dextrocardia should be employed to designate all instances in which the heart is found in the right side of the thorax. If thus employed, the term loses its connotation as a mere anatomical curiosity; and the study of the etiological types of dextrocardia assumes its rightful importance.

The present discussion of dextrocardia in children is illustrated by reports of eight cases. During the course of a study of tuberculosis in school children, in which the author has participated, roentgenograms of the chests of 11,253 children have been made. In this series three cases of dextrocardia have been found, each illustrating a different etiological factor. Another case in which dextrocardia was caused by a marked scoliosis has not been included in this report. Five more cases which have been encountered by the author among children are briefly summarized.

Case Reports

Case 1. A. Z., male, aged 8 (of the tuberculosis research group), referred for physical examination because dextrocardia was found in the roentgenogram. There were no complaints. He is the only child, and the family history is negative. Birth was normal with no cyanosis. He sat alone and had his first tooth at six months, walked and talked at 14 months. He has had measles and scarlet fever. Mantoux negative.

Physical examination corroborated the roentgenographic findings. The cardiac dullness and impulses were on the right side, and the liver dullness on the left. There was no evidence of any pathologic cause for the dextrocardia on either roentgenographic or physical examination. Electrocardiogram showed mirror image inversion of normal Lead I (figures 1 and 2).

Diagnosis: Congenital dextrocardia with situs inversus.

Comment: The occurrence of cardiac misplacement in conjunction with transposition of viscera has long been known. The first reported observation is credited to Petrus Servius [2] in Rome in 1643. It was also reported in Paris in 1650 [2] in the man who was executed for the murder of the Duke of Beaufort, as related by Guy Patin, and later reported in London in 1674. Its incidence has been variously estimated. It is said to be approximately 1 in 10,000. The difficulty in determining the incidence accurately is obvious. However, one case in over 11,000 is here reported. Moffet and Neuhoff [3] reviewed the literature from the year 1649 to 1915 and were able to find only 126 reported cases of true congenital dextrocardia.

A second case of congenital dextrocardia with situs inversus was found

* Received for publication August 10, 1935.

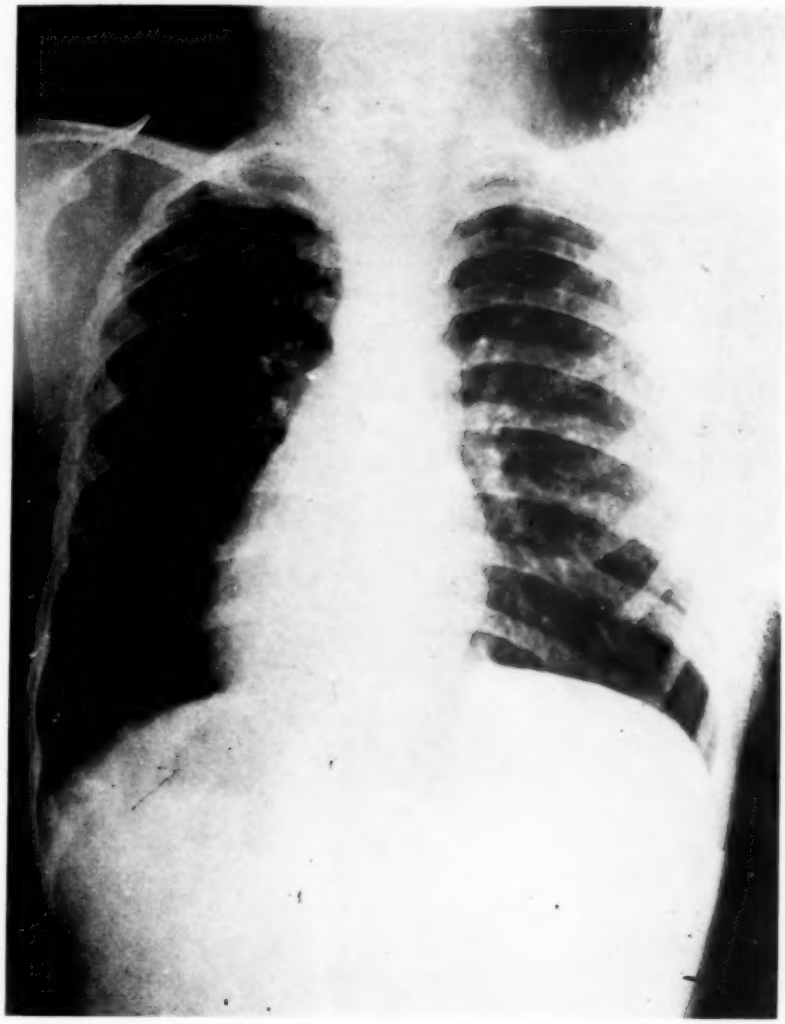

FIG. 1. *Case 1.* A. Z., male, aged 8 years. Congenital dextrocardia with situs inversus.

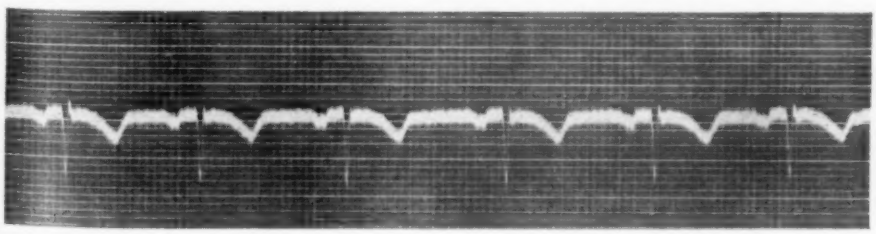

FIG. 2. *Case 1.* A. Z., male, aged 8 years. Mirror image inversion of normal Lead I.

in a child referred to our chest clinic (Pediatric Department, New York Post Graduate Medical School and Hospital).

Case 2. P. M., female, aged 2½ years. The chief complaint was of a chronic cough since birth and of frequent colds.

Physical Findings: 1. Dextrocardia; heart sounds normal; no symptoms referable to the heart. 2. Numerous coarse and fine râles on inspiration on both sides posteriorly with some expiratory coarse râles. 3. Throat congested; marked post-nasal drip; tonsils enlarged and infected.

Laboratory Findings: Roentgen-ray: Chest: 1. Dextrocardia with visceral transposition. 2. Central pneumonic infiltration. Sinuses: Pansinusitis. Mantoux: Negative. Electrocardiogram: Mirror image inversion of normal Lead I.

Diagnosis: 1. Chronic bronchitis. 2. Central pneumonitis. 3. Pansinusitis. 4. Congenital mirror picture dextrocardia with situs inversus.

Comment: As early as 1749 dextrocardia was divided into congenital and acquired groups. Nagel [4] divided the congenital dextrocardias into two main groups: 1. True mirror picture congenital dextrocardia; 2. congenital dextrocardia due to arrest of development.

The exact nature of the pathogenesis of these groups is still not clearly understood.

In true mirror picture dextrocardia the heart is reversed or transposed upon itself, coming to lie on the right side with the relationship of the various structures of the heart to each other remaining both physiologically and anatomically unchanged. The apex points to the right. The apex beat is palpated near the right mammary line and is formed by what is normally the left ventricle, presenting a true mirror picture of the heart. This type of dextrocardia is usually associated with transposition of the other organs or viscera. Congenital mirror picture dextrocardia without transposition of the other viscera (isolated dextrocardia) does occur, but it is exceedingly rare, in which event it is to be differentiated from dextrocardia due to arrest of development. It is possible to have all kinds of combinations of transposition of the viscera. Abernethy [5] in 1793 reported the case of a female infant, 10 months of age, in which the heart was on the right side, the liver in the midline with the rest of the organs in their normal positions. Royer and Wilson [6] report the case of a boy, aged six years, found to have complete transposition of all viscera except the heart which was in its normal position. Even the lungs were included in the transposition. The three-lobed lung was on the left side and the two-lobed on the right.

In congenital dextrocardia due to arrest of development the heart is said to retain the position occupied by it during the early stages of embryonic life, because of an arrest of development. There is no transposition of other viscera. The apex points downward and is formed by the right ventricle. As a result of this arrest of development there is not only a dextrocardia but also grave and complex anomalies of the heart associated with it, such as transposition of the aorta and pulmonary artery and complete

defect of the cardiac septa, as in Wenner's [7] case. There may be many possible combinations of defects, from the slightest to the gravest, either of the large vessels themselves, of the communication between the large vessels and the heart, or of the heart itself. In this type there is usually marked cyanosis, and the prognosis is grave. In uncomplicated mirror picture dextrocardia the sounds are normal; there is no cyanosis or anatomical interference with the heart function; and the electrocardiogram will show the characteristic findings: a mirror image inversion of normal Lead I. On the other hand in dextrocardia due to arrest of development there is only a right sided preponderance.

Case 3. W. F., male, aged 10 years.

Past History: Normal delivery; cyanosis since birth; feeding was difficult. Mother says that as an infant he turned very blue whenever he cried or ate. Had seven attacks of purulent otitis media in the first year of life and was considered "delicate." Mother was told at three months of age that child had a dextrocardia, and at five years of age was told that he had a murmur in addition to the dextro-

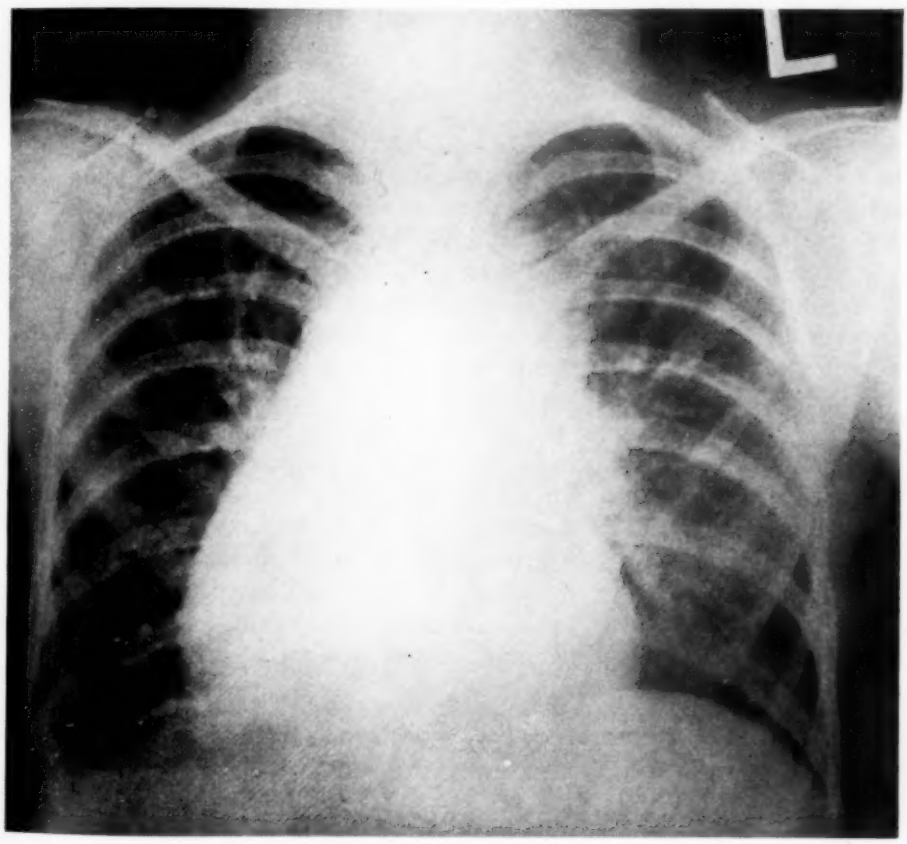

FIG. 3. *Case 3.* W. F., male, aged 10 years. Congenital picture dextrocardia with situs inversus. Congenital heart disease, probably septal defect.

cardia. Had bronchopneumonia at seven years of age, which was associated with marked cyanosis. Measles at eight years; no complications. In February 1935 had left lower lobar pneumonia. Temperature seldom reached 101° by rectum, and pulse was between 50 and 60. There was marked cyanosis, and resolution was delayed. A month later he had a second attack of pneumonia.

Physical Examination: Underdeveloped, pale youngster. Cyanosis of lips and fingertips, no clubbing. Heart impulse felt 11 cm. to the right of the midline. There was a harsh systolic murmur heard at the base and over the precardium. There was no thrill. Lungs were clear. Liver and spleen not palpable.

Fluoroscopic Examination: A. P. View: Heart seen to the right of the midline with general cardiac enlargement. First Oblique (right shoulder to screen) showed enlargement of left ventricle. Second Oblique (left shoulder to screen) showed the retro-cardiac space clear.

Roentgen-ray (figure 3) revealed: 1. Dextrocardia with situs inversus. 2. Enlarged and ovoid type of heart. 3. Accentuated pulmonary markings.

Electrocardiogram: 1. Normal sinus rhythm. 2. Normal A. V. conduction time with occasional sino-auricular block. 3. Right axis deviation of the Q.R.S. 4. Q.R.S. low voltage and notched. 5 Mirror image inversion of normal Lead I. 6. P-wave inverted in all three leads. 7. Abnormal T-wave in Lead I. Conclusion: In addition to a mirror picture dextrocardia these abnormalities indicate myocardial disease with probably some disturbance of conduction through the bundle of His, as indicated by number 4.

Diagnosis: 1. Congenital dextrocardia with situs inversus. 2. Congenital heart disease, probably some septal defect with cardiac enlargement. 3. Myocardial disease in region of the bundle of His.

Comment: The roentgen-ray and the electrocardiogram undoubtedly prove that the dextrocardia is of the true mirror picture type. If this case were seen in the first month of life it would be apt to be confused with dextrocardia due to an arrest of development because of the marked cyanosis. The roentgen-ray alone would be sufficient to aid in differentiation in that it would reveal the situs inversus which is always associated with true mirror picture dextrocardia. The congenital heart lesion (septal defect) which is superimposed upon a true congenital dextrocardia easily accounts for the cyanosis. The patient also has myocardial degeneration probably involving the bundle of His, as shown by the electrocardiogram, which may account for the very slow pulse during his attack of pneumonia. Moffet and Neuhoff [3] report a true congenital dextrocardia with situs inversus also associated with a patent inter-ventricular septum with cyanosis.

The classification of congenital dextrocardia is not sufficiently inclusive from a practical standpoint. This is exemplified in the following two cases which are undoubtedly congenital but have all the characteristics of the acquired type.

Case 4. M. R., male, aged 6 years (of the tuberculosis research group), was referred for physical examination because the heart was found on the right side. There were no complaints, except for an occasional cough. The appetite was good. The delivery was by Caesarian section, and the birth weight was eight pounds. Development was normal both physiologically and physically. He had measles, scarlet fever and whooping cough. There were no subjective symptoms referable

to the dextrocardia or to the condition causing it. Roentgen-ray (figure 4) revealed a definite diaphragmatic eventration with a dextrocardia.

Physical Examination: The apex impulse was in the right mammary line with the cardiac dullness on the right side. There was no evidence of transposition of other viscera. Normal liver dullness was elicited on the right side. There was definite increase in resonance with diminished respiratory sounds at the left base. Both child and parents were uncoöperative. They disappeared when a fluoroscopy with barium was prepared and repeatedly broke appointments for both a fluoroscopic and electrocardiographic examination. Mantoux test was positive.

Diagnosis: Dextrocardia secondary to eventration of diaphragm.

Comment: Baynes-Jones [8] tabulated 45 cases of eventration of the diaphragm from the literature. The great majority occurred in males. Three

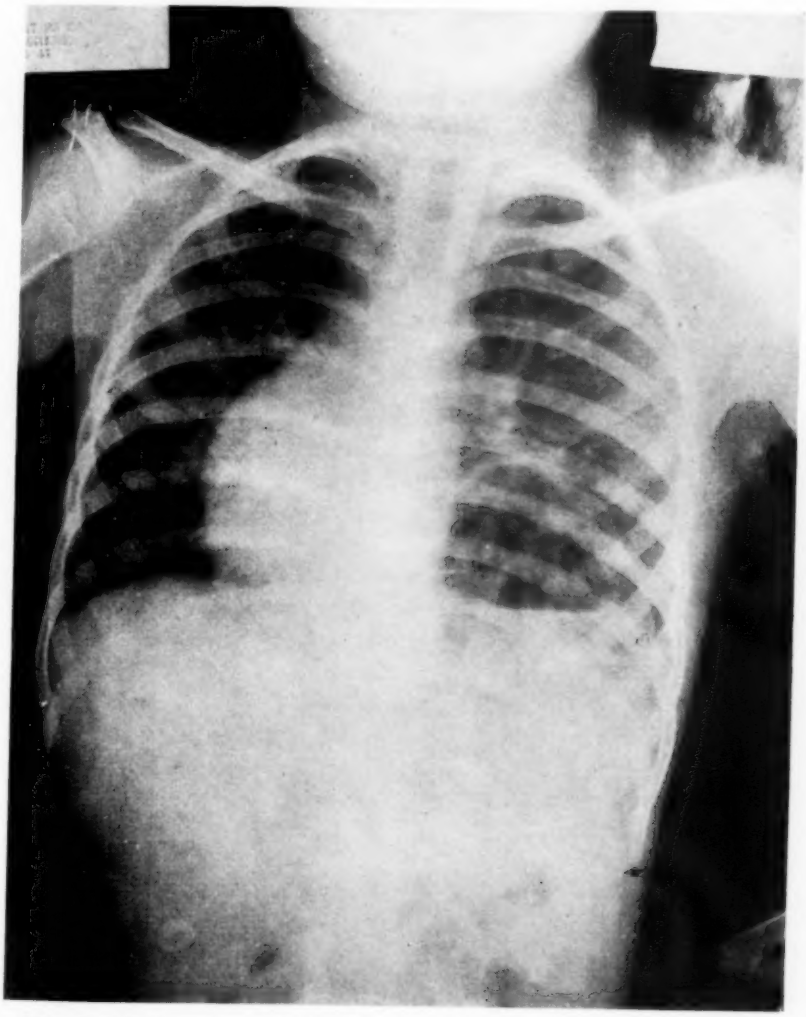

FIG. 4. *Case 4.* M. R., male, aged 6 years. Dextrocardia secondary to eventration of the diaphragm.

were right-sided lesions, while 42 were on the left side. He states: "In eventration the diaphragm is greatly thinned as well as distended, and there is no solution of its continuity. In this essential respect the condition is different from hernia of the diaphragm which, whether true or false depending upon the presence or absence of the hernial sac, consists of a localized opening in the sheet of the diaphragm through which the abdominal viscera pass into the thoracic cavity."

Blackford and Booth [9] in 1932 reported a case of dextrocardia secondary to eventration of the diaphragm identical to the one here reported. The electrocardiogram was normal. Landis [10] says concerning eventration: "That eventration is a congenital abnormality is apparent. As the condition is congenital both the thoracic and abdominal viscera accommodate themselves to the defect, and as a result there are no symptoms." That the condition is not always congenital, however, is evidenced by Hedblom's [11] case of dextrocardia secondary to eventration of the diaphragm presumably due to neuritis of the phrenic nerve with evidence of neuritis elsewhere in the extremities. Both the diaphragm and the heart eventually resumed their normal position. Landis further states: "The condition may be suspected on physical examination, but in most instances it is discovered as a result of the roentgen-ray examination or at the autopsy table." Of physical signs he says: "In left-sided cases the most striking sign is the abnormally large area of tympany both anteriorly and posteriorly. Owing to the large area of tympany the condition most likely to simulate eventration is pneumothorax or congenital hernia. Among the more unusual conditions are large basal cavity and subphrenic abscess producing gas. As eventration never gives rise to any disturbance and is usually an accidental discovery it requires no treatment." Although eventration is considered a harmless condition it may, however, have very serious consequences. Blackford and Booth [9] quote a case that ended fatally. A young woman had been healthy until several months' pregnant. In the examination because of the abdominal symptoms which developed at that time it was found that she had an eventration on the left side with the heart displaced to the right. She would not consent to an abortion, and during labor which was premature a complete rupture of the diaphragm and death occurred. It is conceivable, therefore, that any condition, such as whooping cough, which could produce a marked increase in intra-abdominal pressure might cause a rupture of the weakened diaphragm. Similarly it is possible that eventration may also be acquired from a congenitally weak diaphragm.

Case 5. L. D., colored female, aged 1½ years, admitted 9/10/34 on Pediatric Service, Jamaica Hospital. Died 9/11/34.

Past History: Patient well until day before admission when she refused nourishment and vomited the little she took. No bowel movement in the last 36 hours. Two enemas given daily before admission: first yielded some fecal material, second returned clear. Has vomited all food taken day of admission. There was no fever. She received nothing but water in the 24 hours prior to admission. Later additional his-

tory revealed that only liquid food was given the child since birth, and that just prior to the onset the child was given ham and eggs.

Physical examination revealed: 1. Acetone odor to breath. 2. Malnutrition. 3. Heart sounds and impulses on the right side. 4. Some diminution of breath sounds on the left side with dullness on percussion in the lower part of the chest. 5. Marked distention with dullness on percussion over upper left quadrant. Remainder of abdomen not distended. A nasal tube was passed and 17 ounces of clear fluid were obtained following which distention disappeared. 6. Albuminuria. 7. Leukocytosis of 15,600 with 74 per cent polynuclear cells.

FIG. 5. *Case 5.* L. D., female, colored, aged 1½ years. Dextrocardia secondary to congenital diaphragmatic hernia.

Roentgenogram (flat plate of abdomen and chest) (figure 5): 1. Dextrocardia. 2. Hernia of left diaphragm.

Diagnosis: Congenital diaphragmatic hernia with secondary dextrocardia.

The general condition of the child became rapidly worse. It was decided to operate without delay. At operation the stomach was found to be rotated about one inch proximal to the pylorus. The stomach was greatly distended and displaced

upward into the left thoracic cavity together with the transverse colon, spleen and coils of small intestine. The diaphragm was totally absent on left side, there being only reflections of peritoneum about one-half inch wide on either side with some muscular fibers around central dome. The child died several hours after the operation.

Autopsy corroborated the operative findings: 1. Massive collapse of left lung. 2. Displacement of heart to the right. 3. Fatty degeneration of liver. 4. Herniation of left diaphragm. 5. Repair of left diaphragmatic leaf.

This is undoubtedly a congenital hernia (false) because of the almost complete absence of the diaphragm, the absence of a history of violent injury, and evidence that the collapse of the lung had existed for a long period.

Comment: Diaphragmatic hernias are classified either as congenital or acquired, and are further classified as true or false depending upon the presence or absence of a sac. The congenital hernia is due to incomplete development of the diaphragm. The acquired hernia develops after birth in a congenitally weak area similar to the development of a hernia elsewhere and obviously has a sac except those of traumatic origin due to violent injury, gunshot and stab wounds.

The signs of hernia are varied and inconstant. The first symptom may be manifest soon after birth and be either respiratory or gastrointestinal, or it may develop in later life, as in this child, with symptoms of obstruction which were produced by torsion of the stomach above the pylorus. One must appreciate the various possible signs that could be produced by the stomach filled with air or fluid, the large and small intestines and possibly the spleen, all or part of which may be in the chest cavity, most commonly on the left side. The symptoms may include any combination of the following: cough, dyspnea, cyanosis, decreased respiratory movement on the affected side, bulging of the chest, absence of respiratory murmur and signs of either fluid or pneumothorax. The abdominal signs may be vomiting, nausea, unusually flattened abdomen and signs of obstruction. A dextrocardia should always stimulate a search for diaphragmatic hernias since these are frequently the cause of displacement of the heart to the right side. Following successful repair of the hernia the heart returns to its normal position.

The most important and difficult differentiation to make is that between diaphragmatic hernia and eventration. According to Giffin [13] the term eventration was first used by Petit in 1790 and applied to the condition of chronic idiopathic unilateral elevation of the diaphragm. He considers it a most unsatisfactory term. Eventration is defined as "protrusion of the bowels through an opening in the abdominal wall." Hernia is defined as "the protrusion of an organ or part of an organ or other structure through the wall of a cavity normally containing it." Giffin feels that the terms might easily be interchanged and perhaps rightly so. Since all true hernias must have a sac and since most congenital diaphragmatic hernias and those acquired of traumatic origin have no sac, it would not only be more descriptive but also anatomically correct were the terms to be reversed.

There has been a marked increase in the cases diagnosed and reported in recent years. This is due chiefly to the advance in roentgenologic diagnosis.

The diagnosis rests chiefly and finally on roentgenologic examination. Some hernias are spontaneously reduced in the upright position. Hence, if there is any doubt as to the diagnosis it is advisable to make the roentgenologic examination in either the horizontal or Trendelenburg position. Once the diagnosis is made, surgical intervention should follow, because the mortality is much higher in complicated cases such as the one above reported. The operative mortality has been greatly reduced in recent years. Hedblom [14] states that among 57 cases reported during the last three years the immediate result was good in 72 per cent. There were eight deaths, a mortality of 14 per cent.

This type of dextrocardia is not generally included in the classification of congenital dextrocardias. Dextrocardia secondary to congenital diaphragmatic eventration or hernia is obviously congenital, but it is caused by pathologic conditions similar or identical in principle to the dextrocardias of acquired origin. Since the term congenital merely means to be born with, I think it is preferable that this type of case be classified as "congenital dextrocardia with acquired characteristics." Paradoxical as it may appear I feel that it is quite descriptive. Jones [15] gives a similar classification for this group. By dextrocardia of acquired origin is meant a heart which has been displaced to the right from the normal left-sided position which it had occupied, by some pathological process.

The following cases illustrate the acquired type.

Case 6. M. M., colored female, aged 10 years (of the tuberculosis research group), was referred for physical examination because of marked disease in the right lung and a dextrocardia. On inquiring whether there were any complaints we were told "just pain in the chest" and "hoarseness."

Family History: Father and mother in good health. Five children, none dead, no history of tuberculosis in the family.

Past History: Normal birth, no asphyxia or cyanosis, normal development, first tooth at five months, walked at nine months and talked at one year. Had measles and whooping cough. The mother stated that the child had no respiratory trouble.

Physical Examination: Malnourished in appearance, enlarged cervical lymph nodes, foul breath, tonsils large, cryptic, almost meet in the midline. Chest is narrow, asymmetrical; right chest is smaller and retracted; marked Harrison's groove; impairment of resonance over whole right chest with fine and large moist râles scattered throughout, particularly the upper half. The breath sounds increased on the right side. There was a hyperresonant note on the left side. The apex beat was on the right side near the nipple line in the fourth interspace about 5 cm. from the mid-sternal line. Four tuberculin tests (Mantoux) with increasing strengths were negative (the strongest dilution being 1–10).

Electrocardiogram: 1. Normal sinus rhythm. 2. Normal A. V. conduction time. 3. Neither right nor left axis deviation.

Fluoroscopic examination corroborated the roentgenographic (figure 6) findings of dextrocardia and marked right-sided pulmonary disease. There was retraction of the right chest with diminished respiratory movements. Bands of pleuro-pericardial adhesions were distinctly visible which were undoubtedly binding the heart to the right side.

Diagnosis: Non-tuberculous fibrosis of the right lung with pleuro-pericardial adhesions causing dextrocardia.

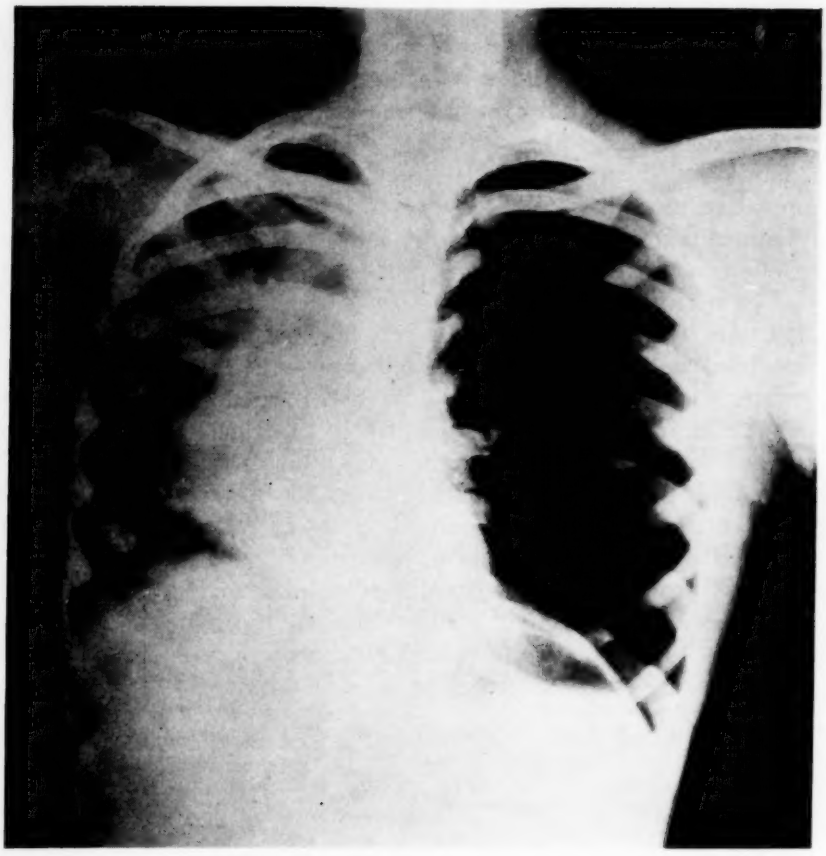

FIG. 6. *Case 6.* M. M., female, colored, aged 10 years. (May 1, 1933.) Dextrocardia secondary to pulmonary infiltration and pleuro-pericardial adhesions with emphysema of the left side.

It was difficult at the time definitely to rule out a pneumothorax. The absence of the retracted visceral pleural line that is seen in pneumothorax, the findings on fluoroscopy, particularly the pleuro-pericardial adhesions, the persistence of the dextrocardia to date since first noted in May 1933 (patient was reëxamined in April 1934, and dextrocardia was still present but with somewhat diminished pulmonary infiltration on the right side) and the subsequent course leave little doubt as to the diagnosis. On November 19, 1934, she was admitted to the children's ward in Jamaica Hospital with an extensive bronchopneumonia on the left side and dextrocardia. After the bronchopneumonia had subsided the dextrocardia still persisted. At this time the child was again fluoroscoped, and the pleuro-pericardial adhesions were visible on the right side.

The following case of dextrocardia in an adult was similar to but much

more advanced than the case just reported, and the report of autopsy is available.*

Case 7. L. G., male, aged 42 years. Admitted Dec. 9, 1932; died Dec. 28, 1932. Chief complaint: Dyspnea and orthopnea.

Present Illness: Hacking cough, productive, started two weeks ago. Had similar attack two and one-half years ago. During recent attack feet were swollen. The swelling decreased when he stayed in bed.

Past History: About 12 years ago patient first noticed that he became short of breath and about that time developed a cough, at first dry but later productive.

Physical Examination: On admission temperature 99.8° F., pulse 96, and respirations 30. The patient is a well nourished adult male, perspiring and coughing persistently, forcefully and productively.

Chest: Impairment of resonance on right side with increased vocal and tactile fremitus along entire right side anteriorly and posteriorly. There are numerous crackling râles at the right base. Heart: Maximum impulse felt in the third right interspace 8 cm. from mid-sternal line. First sound moderately loud and short. Faint systolic blow and short presystolic murmur.

Roentgen-ray diagnosis: 1. Dextrocardia. 2. Chronic infiltrative process in the right lung with retraction of chest wall and displacement of the trachea. 3. Small exudate in right chest. 4. Chronic bronchitis and bronchiectasis of left lung.

Electrocardiogram: Normal rhythm. No mirror inversion image in Lead I. Left axis deviation of the Q.R.S. T_1 and T_2 are diphasic. There are premature ventricular beats in Leads II and III.

Clinical conclusion: Ventricular myocardial disease.

Patient became progressively worse with a rising temperature and died Dec. 28, 1932.

Summary of autopsy findings: 1. Non-tuberculous fibrosis of right lung, incident to old interstitial pneumonia with pleuro-pericardial adhesions; compensatory enlargement of left lung with minimal apical fibrosis, diffuse suppurative bronchitis and bronchopneumonia. 2. Dextrocardia with cardiac hypertrophy and dilatation. 3. Cirrhosis of spleen and kidneys. 4. Chronic passive congestion of spleen and kidneys. 5. Supernumerary nipple.

Cause of death: Bronchopneumonia.

Diagnosis: Dextrocardia secondary to non-tuberculous fibrosis of the right lung and pleuro-pericardial adhesions.

Comment: I have added this adult case, not only because of its autopsy findings, but also by way of complement to the preceding case of M. M., aged 10 years, also with dextrocardia, pleuro-pericardial adhesions and pulmonary infiltration. It pictures to us the probable outcome of the child in the not too distant future. In both cases there was considerable compensatory emphysema of the left lung. It is difficult to say how much of the cardiac displacement is due to the emphysema. It is easily conceivable that it does exert some force. If that is so, then there are two distinct forces exerted in the same direction in displacing the heart to produce the above type of dextrocardia; fibrosis of the lung with fibrous bands causing traction, or a pulling force on the heart, and an emphysema pushing the heart to the right.

* This case was on the service of Dr. Carl Boettiger, at the Mary Immaculate Hospital, Jamaica, to whom I am indebted for permission to report it.

Case 8. G. W., male, aged 21 months.

Past History: Irrelevant.

Present Illness: Ill for about one week prior to admission to hospital January 22, 1935, at which time he was extremely ill, cyanotic, dyspneic. Temperature 100°. Evidence of consolidation of the left lower lobe. Five days after admission showed evidence of fluid in the left chest. Fluid increased very rapidly with evidence of cardiac displacement to the right. Paracentesis performed and pus was removed from the left chest. Roentgen-ray revealed evidence of a great deal of fluid in the left chest with considerable displacement of the heart and trachea to the right. Child was operated upon immediately for empyema, made a good recovery, and heart returned to its normal position.

Diagnosis: Dextrocardia secondary to empyema on the left side.

Comment: The causes of acquired dextrocardia are many. Any condition which can cause displacement of the heart to the right side can produce a dextrocardia. In its normal position approximately two-thirds of the heart lies to the left. Obviously there may be various degrees of dextrocardia from partial to complete. Among the numerous conditions reported causing dextrocardia are: On the right side—tuberculous fibrosis, non-tuberculous fibrosis, pleuro-pericardial adhesions, atelectasis and carcinoma. (In 16 cases of acquired dextrocardia reported by Hedblom [11] three were due to carcinoma of the right lung.) On the left side—diaphragmatic hernia and eventration, tumor or cysts of the lung, fluid in left chest and pneumothorax. Miscellaneous causes include scoliosis, megalocolon and mediastinal emphysema. The symptoms naturally are dependent upon the underlying cause.

Summary

Eight cases of dextrocardia are reported, three of which were discovered in a series of 11,253 roentgen-rays of children's chests. These eight cases were as follows:

1. A true mirror picture dextrocardia with situs inversus.
2. Dextrocardia secondary to congenital eventration of the diaphragm.
3. Acquired dextrocardia secondary to pleuro-pericardial adhesions with non-tuberculous infiltration of the right lung.
4 and 5. Two additional cases of true congenital mirror picture dextrocardia, one of which was associated with a patent interventricular septum, cyanosis and myocardial disease involving the bundle of His.
6. Dextrocardia secondary to congenital diaphragmatic hernia.
7. Dextrocardia secondary to non-tuberculous fibrosis and pleuro-pericardial adhesions in an adult with autopsy findings.
8. Dextrocardia secondary to empyema on the left side.

A modified classification of dextrocardia is proposed:

I. Congenital
   1. True mirror picture dextrocardia: (*A*) with situs inversus; (*B*) isolated congenital dextrocardia without situs inversus.
   2. Dextrocardia due to arrest of development.

3. Congenital dextrocardia with acquired characteristics, as that secondary to congenital diaphragmatic hernia, eventration or atelectasis.

II. ACQUIRED

1. Dextrocardia developing after birth secondary to acquired conditions.

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THE LETHAL EFFECTS OF SOLAR RADIATION ON GUINEA PIGS *

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DURING the last 15 years, a few reports have appeared in the literature in which it was stated that mammals, and particularly rodents, died sometimes when exposed to solar radiation for relatively short periods of time. That radiant energy in certain parts of the spectrum may be lethal for photosensitized animals is well known; but it is interesting to note that several authors were surprised when they observed the lethality of solar insolation for nonsensitized animals. The hitherto published work is based on essentially qualitative studies; none satisfied even elementary physical considerations. There are no adequate measurements of the power † of the radiant energy that is lethal under the conditions of the particular experimental situation, nor are there any measurements of the spectral distribution of the radiant energy incident upon the test animals. Furthermore there are only totally inadequate attempts to determine the potential dependence of the phenomenon upon variations of the spectral composition of the incident energy. The descriptions of the pathological changes in the test animals are incomplete and controversial.

We stumbled on the observation that guinea-pigs were sensitive to radiant energy and that they died regularly within an hour when exposed to the midday sun at Tucson, Arizona (altitude 2,600 feet, latitude 32° 15′ North), even at the time of the winter solstice. Since bibliographical search showed us that this phenomenon was little known, that the observed data were inadequate and that the conclusions drawn from them were often erroneous and misleading, we decided to study this condition. Our decision was encouraged by two considerations: (1) that in the Research Institute of the Desert Sanatorium in Tucson we had at our disposal physical apparatus and meteorological conditions suited for such experimental studies, and (2) the thought that the physiological effects of absorbed radiant energy could be studied to best advantage under conditions in which the observable *status quo* is not maintained, i.e., in which physiological compensation is inadequate, rather than the reverse; for complete compensation often obscures the changes initiated by the stimulus. Therefore, the apparent sensitivity of rodents to powers of radiant energy seemed a fertile object for the study of physiological effects produced by this form of energy.

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† The term power is used in this paper in its correct physical sense, meaning "rate of flow of energy; i.e. Power $= \frac{\text{Energy}}{\text{Time}}$."

The experimental apparatus consisted of a Foucault siderostat, carrying a 12-inch square stellite mirror mounted in a dome connected by a passageway with a windowless room free of drafts. The radiant energy of the sun is reflected by such a siderostat in a constant direction; in this instance into the adjoining room, regardless of the changing altitude and azimuth of the sun. The radiation was passed through a 12-inch fused quartz lens of approximately two meter focal length. The shaved ventral surfaces of the guinea pigs were exposed at right angles to the beam through a slit of constant dimensions (2″ by 4″). A thermocouple was mounted in the plane of the animal and was connected with a galvanometer of suitable characteristics. The deflections of the latter in response to radiant energy incident upon the receiving surface of the thermocouple had been calibrated for conversion into absolute energy units. Variation in the power of the incident energy was obtained by translational movement of the animal toward or away from the focal point of the quartz lens. Fractionation of the spectrum was accomplished by the interposition in the beam of solar radiant energy of suitable quartz, glass, and liquid filters whose transmission characteristics had been determined by standard spectrometric methods.

Over 100 animals were exposed to various powers of radiant energy of the following spectral compositions:

(*a*) 0.30 μ–3.0 μ (integrated solar radiant energy at Tucson) (34 animals).
(*b*) 0.30 μ–1.4 μ (integrated solar radiant energy minus "far infra-red") (11 animals).
(*c*) 0.37 μ–3.0 μ (integrated solar radiant energy minus "ultra-violet") (14 animals).
(*d*) 0.37 μ–1.4 μ (integrated solar radiant energy minus "far infra-red" and "ultra-violet") (6 animals).
(*e*) 0.34 μ–0.66 μ (practically only "visible") (24 animals).
(*f*) 0.62 μ–3.0 μ (practically only "near" and "far infra-red") (11 animals).
(*g*) 0.62 μ–1.4 μ (practically only "near infra-red") (14 animals).
(*h*) 1.0 μ–15.0 μ (practically only "far infra-red") (9 animals)—(Artificial source of radiant energy used in this instance).

In each of the above spectral regions, we determined (with due consideration of such variables as body weight, room and body temperature and skin pigmentation) the minimal powers of radiant energy to which the animals regularly succumbed within one hour; they are approximately of the magnitude of those of unconcentrated solar radiation at Tucson. These figures were then corrected for losses by reflection at the surface of the animal. The detailed data will be published elsewhere. Here we wish to report only that *each of the above arbitrary divisions of the solar spectrum can be lethal for guinea pigs* and to describe the clinical and pathological findings, which were remarkably uniform and which, with the exception of

minor details, appeared to be *invariant under variation in spectral composition of the radiant energy to which the animals were exposed.*

Under experimental conditions such that death occurs in about one hour, the respiratory rate usually begins to accelerate within 10 minutes after the onset of the exposure, and often attains rates in excess of 180 per minute within 30 or 40 minutes; then the respiration drops suddenly to less than the normal rate and becomes markedly irregular and grunting. The impression was gained that during the last few minutes of life, there develops a discoördination of the respiratory musculature, in the sense that inspiratory and expiratory muscles contract simultaneously. The animals die usually within 10 or 15 minutes following the drop in their respiratory rate.

The rectal temperatures rise rapidly to 108° F. or more, usually within 45 minutes. At the time of death the rectal temperature is, in most animals, above 110° F. When the exposure was interrupted after the animal had reached 108° or 109° F., the temperature dropped to normal within less than an hour, and often subsequently to subnormal figures, but the animal died, as a rule, within the next 12 or 24 hours.

In animals that died during the exposure, that is within one hour, or shortly afterwards, the gross autoptic findings were quite uniform throughout. The exposed portions of the skin showed numerous petechiae, the subcutaneous tissues were edematous and congested. The lungs showed areas of massive congestion irregularly scattered throughout the parenchyma, apparently unrelated to the posture of the animal during the exposure. A few animals had a slight amount of free blood in the pleural cavities. The left heart was maximally contracted, the right heart was maximally dilated, a finding characteristic of peripheral vascular paralysis. The liver was diffusely congested, and the gall-bladder was always distended with clear bile if the animal had died during the exposure, but when death was delayed for 10 minutes or more the gall-bladder was found empty. The spleen was moderately or markedly congested, and all the splanchnic vessels were distended with blood. Loops of the intestines and part of the anterior gastric wall directly beneath the abdominal wall had patchy areas of hemorrhagic discoloration and edema, and in some animals there was evidence of hemorrhagic infarction in these areas. The kidneys and adrenals showed varying degrees of congestion. The brain showed no abnormality.

Histological studies revealed a number of different lesions in the lungs, namely: (1) massive capillary hyperemia, (2) capillary intraalveolar hemorrhages, (3) small areas of predominantly interstitial lobular pneumonias whose exudate consisted of histiocytes, polymorphonuclears and red cells, (4) scattered, chiefly subpleural, areas of emphysema, (5) markedly contracted bronchial musculature, (6)) desquamation of bronchial epithelium, and (7) edema and lymph stasis in the septa. In the involved areas of the gastrointestinal tract, we found simple hyperemia, particularly in the submucosa, massive edema of the same layer, capillary stasis, hemorrhagic in-

farctions and localized complete necroses. Sections through the exposed portions of the abdominal wall showed small cutaneous extravasations, massive subcutaneous edema and, in cases of delayed death, degenerative changes in the superficial layer of muscle fibers. The other organs showed no pathological changes, with the exception of marked congestion.

Discussion

As was mentioned before, previous reports on the lethal effect of radiant energy on mammals both in regard to its physical foundation and to its pathological results are incomplete. In no instance was there measurement by standard physical methods of the power of the radiant energy incident upon the experimental animal. A few authors recorded and reported the readings of mercury in glass-thermometers, the bulbs of which were exposed to the radiant energy incident upon the test animal. Such readings are not at all an absolute measure of the incident radiant energy, but merely represent the equilibrium temperature attained by the glass bulb of the thermometer in contact with the air surrounding it, which in turn depends upon the fractions of the incident energy that are absorbed by the glass bulb and by the air, which vary with the wave-length as well as with the power of the incident energy. For equal powers of radiant energy, a mercury-in-glass-thermometer gives different readings in different parts of the spectrum in which its absorptivity differs. Since no author recorded in absolute units the powers of the radiant energy to which they exposed their animals, their results cannot be compared. If, as was reported in several instances, the results of experiments with artificial sources of radiant energy did not agree with those with solar insolation, that can only mean that in the one instance the flow of radiant energy did, and in the other did not, exceed that rate for which the test animal under the conditions of the experiment could compensate. For, a logical analysis makes it clear that in any given set of conditions, *there must be some rate of flow of incident energy which no animal can survive indefinitely.* No system which is not in energy equilibrium with its environment can maintain its status quo, i.e., a change of state must occur. Since there are physiological limits to the rate at which a given animal can dissipate energy, the problem resolves itself into the determination of that power of incident radiant energy for which the test animal can compensate by an adequate dissipation of energy. If energy intake is continuously greater than energy output, death must eventually occur.

The surprising thing is that the power of unconcentrated solar radiant energy at many places on the earth's surface is of such an order that the compensatory physiological mechanisms of rodents cannot cope with it, not even for relatively short periods of time.

No author has reported or apparently measured the spectral distribution of the radiant energy to which he subjected his experimental animals; in

fact, several used identical sources, but fixed their attention on one zone of the spectrum while disregarding others present. For instance, some authors used the mercury-vapor-lamp as a source rich in "ultra-violet," while others used the same instrument as a source rich in "visible light"—both neglecting the fact that as much as 40 per cent of the total energy of an average mercury-vapor-lamp may be emitted as radiant in wave-lengths longer than 8,000 Å (i.e., "infra-red").

One of the main points of discussion in the literature is the question whether the lethal effect of irradiation is due to the "thermic rays," the "light rays" or the "actinic rays." These terms are both ambiguous and misleading. Ambiguous, because they do not denote well defined spectral regions, but only approximate ones. Misleading, because radiant energy is neither "thermic" nor "luminous" nor "actinic" until it is absorbed: whether a given quality and quantity of radiant energy upon absorption will (*a*) increase the average kinetic energy of the absorbing molecules (i.e., raise the temperature of the absorbing substance), (*b*) be perceived as light if it falls on the retina, or (*c*) disrupt molecules (i.e., initiate a chemical change) is *dependent upon the characteristics of the absorbing medium as well as that of the radiant energy.* The term "light" should be restricted to the sensation resulting from stimulation of the retina. For example, if radiant energy of say 4,500 Å wave-length falls upon the retina, a sensation of light is experienced; if it falls upon a photographic plate, a chemical change is initiated; and finally if it is directed upon a layer of platinum black, a rise in temperature will ensue, i.e., appear as heat. It remains to be discovered what the response of the skin is to radiant energy of different wave-lengths; but the fortuitous differentiation of the spectrum dependent upon a specialized end-organ, such as the retina, should not be superimposed on other receptors, such as the skin. If the radiant energy of wave-length 6,000 Å stimulates the retina, and 8,500 Å does not, it does not follow that these spectral regions will produce dissimilar effects in the skin. Whether they do or do not, remains to be determined, and should not be prejudged by labels such as "heat" and "light." Since it is apparent that there must exist for radiant energy of any wave-length *that is absorbed* in no matter what small percentage, some power of incident energy which the test animal cannot survive indefinitely, the problem is therefore not whether the "light rays" or the "heat rays" or the "actinic rays" can be lethal, but what the minimum lethal power is in the various parts of the spectrum under a given set of experimental conditions. This we have determined and the results will be published elsewhere.

The physiological mechanism by which absorbed radiant energy causes death is still unknown and must, for the present, remain a matter of speculation. All of the authors who observed the lethal effect of radiant energy noted that death was, in every instance, accompanied by a hyperthermia often exceeding 110° F. The question therefore arises as to whether death

occurs solely because of the production of a hyperthermia. Our findings can be analyzed to give direction for further study. Although we have confirmed that fever is one of the outstanding manifestations, it is not high enough in all animals to cause death per se. In this connection it might be significant, too, to point out again that under appropriate experimental conditions animals die hours after they have regained their normal temperature. It remains to be determined whether the hyperthermia is due simply to the conversion of radiant energy into heat (i.e., an accumulated energy imbalance) or whether it is due, at least in part to indirect causes, such as the liberation of fever-producing substances in those tissues that absorb the radiant energy, or due to a specific physiological derangement of the temperature regulating mechanism by some action of the absorbed radiant energy.

The morphological findings are suggestive of two sets of action: (1) one that is limited to the regions in which radiant energy is undoubtedly absorbed, such as the exposed skin, the underlying subcutaneous tissue and muscle fibers and, apparently the gastric and intestinal walls adjacent to the abdominal wall; and (2) one that is apparently independent of the localization of the incident energy. The direct action is an intense inflammatory stimulus whose initial effect is a marked increase of the permeability of capillaries; for in the regions of direct action we find edema, blood stasis and its sequences all the way to infarction and necrosis. The medium by which the indirect action is conveyed is unknown. Since the skin is undoubtedly severely injured, since the pathological picture is that of generalized vascular paralysis, with practically universal arteriolar and capillary dilatation, since the lungs show patchy emphysema and contraction of bronchial musculature, it is inviting to ascribe the indirect effects to histamine-like substances that may be liberated in the regions of direct action. This is, as yet, no more than a speculation which is, however, susceptible of experimental confirmation.

The most surprising morphological finding is the occurrence of pneumonic lesions in the lungs; these have not been previously recorded. Although it can never be proved that they did not antecede the exposure, we can state definitely that they were present in the majority of all animals killed by radiant energy and that they were absent in all control animals, including those that were treated in exactly the same way as the test animals, except that they were not irradiated. The conclusion seems, therefore, inescapable that they were caused by the absorbed radiant energy. Since these pneumonic lesions were found in animals whose abdomens only were irradiated, they must probably be ascribed to the indirect effects.

Conclusions applicable to man must be drawn with great caution from these experiments, because man has vastly more efficient compensatory mechanisms than has the guinea-pig. The latter has practically no sweat glands, its normal respiratory rate is relatively high so that increased dissi-

pation of heat by increased respiration is quite limited; furthermore its skin is very thin so that radiant energy penetrates probably relatively deeper.

On the other hand it is apparent that the initial tissue alterations caused by radiant energy are essentially the same in all mammals.

It is probably significant that pulmonary hemorrhages are a constant finding; this may be looked upon as an experimental confirmation of the empirical opinion that insolation may produce hemoptysis in patients with pulmonary lesions. Some of the other findings in our experimental animals bring to mind two clinical conditions in man, namely the so-called "Sonnenbronchitis" of some German authors and the so-called "summer-pneumonias." But since these two diseases are not generally accepted as clinical entities, and since their pathological substrata are unknown in the first, and not well established in the second disease, we wish only to mention that our findings may possibly have some bearing on these conditions in man.

These studies present, as far as we know, the first experimental proof that radiation in the spectral region 0.34 μ–0.66 μ (i.e., almost coinciding with the region called "visible") can produce profound biological effects in non-sensitized animals. In particular, the lethal effect of radiation on mammals in the few instances that have been previously reported, has been uniformly ascribed either to the "ultra-violet" or the "infra-red" portions of the spectrum.

Summary

That mammals, and particularly rodents, may be killed by radiant energy without previous photosensitization, has been observed by a few workers. This phenomenon has, however, never been studied thoroughly, and no attempts have ever been made to measure adequately the incident radiant energy both as regards the minimal lethal power and its spectral distribution.

In experiments that fulfilled these basic physical requirements, the authors have shown:

1. Guinea pigs whose shaved abdomen, or thorax, or both is exposed to a sufficient power of solar radiant energy die within one hour with a characteristic sequence of clinical phenomena.

2. The power of radiant energy required for this lethal effect is of the magnitude of solar radiation existing at an altitude of 2,600 feet and a latitude of 32° 15′ North.

3. The spectral regions for which this lethal effect has been proved are as follows:

(*a*) 0.30 μ–3.0 μ (integrated solar radiant energy at Tucson) (34 animals).
(*b*) 0.30 μ–1.4 μ (integrated solar radiant energy minus "far infra-red") (11 animals).
(*c*) 0.37 μ–3.0 μ (integrated solar radiant energy minus "ultra-violet") (14 animals).

(*d*) 0.37 μ–1.4 μ (integrated solar radiant energy minus "far infra-red" and "ultra-violet") (6 animals).
(*e*) 0.34 μ–0.66 μ (practically only "visible") (24 animals).
(*f*) 0.62 μ–3.0 μ (practically only "near" and "far infra-red") (11 animals).
(*g*) 0.62 μ–1.4 μ (practically only "near infra-red") (14 animals).
(*h*) 1.0 μ–15.0 μ (practically only "far infra-red") (9 animals)—(Artificial source of radiant energy used in this instance).

4. The pathological findings in the animals that succumbed to the effects of radiant energy are as follows:

Massive congestion of lungs, liver, spleen, splanchnic vessels, of those parts of the gastrointestinal canal and of the subcutaneous tissue that lie directly beneath the exposed skin surface; less marked and less constant congestion of kidneys, adrenals and testes. Maximal contraction of the left heart and maximal dilatation of the right heart.

Histologically, small lobular, mainly interstitial pneumonias are frequently seen; associated with these lesions and with irregularly distributed regions of intense capillary congestion, are intraalveolar hemorrhages, patches of mainly subpleural emphysema, contracted bronchi. The intestinal loops and the anterior wall of the stomach show frequently, in addition to massive congestion, stasis, submucous edema, localized hemorrhagic infarctions and necroses.

OCCURRENCE OF MACROCYTIC ANEMIA IN ASSOCIATION WITH LESIONS OF THE BOWEL*

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It is well known that a variety of conditions are often accompanied by a morphologic blood picture resembling, and often indistinguishable from, the blood picture of pernicious anemia. Conspicuous among these conditions are instances in which the intestinal tract is involved in some disease process. This study was undertaken to determine, if possible, just what lesions of the ileum and cecum are likely to be accompanied by an anemia which resembles pernicious anemia.

The first case in which pernicious anemia probably was secondary to an intestinal disturbance was reported by White, in 1890. At necropsy, ulcerative and cicatricial lesions were found in the colon. Faber (1895), according to Strauss, reported the first case in which a blood picture of pernicious anemia apparently was the result of an anatomic abnormality. Two fibrous strictures of the small intestine were found at necropsy. These strictures were probably secondary to a healed tuberculous process. In 1897, Faber reported another case of pernicious anemia which was associated with intestinal obstruction. Since this time blood pictures which are characteristic of pernicious anemia have been reported in cases in which there were various organic abnormalities of the intestinal tract. Seyderhelm, Lehmann, and Wichels (1924) produced a stenosis in the small intestines of dogs, and in two of the 10 animals the blood picture resembled that of pernicious anemia. These same workers (1927) mention a case in which pernicious anemia developed secondary to a stricture of the small intestine. When the stricture was surgically eradicated the blood picture became normal. Little, Zerfas, and Trusler (1929) reported the development of the blood picture of pernicious anemia in a case in which there was a stricture of the small intestine. The anemia, however, was not relieved when the bowel was restored to its normal state. In a review of the literature, in 1929, Meulengracht found 22 cases in which pernicious anemia apparently was the result of organic abnormalities of the intestinal tract. In 18 of these cases there was a stricture of the small intestines, in three there was a stricture of the colon, and in one there was a stricture of the cecum. Schlesinger (1933) observed a case in which pernicious anemia occurred secondary to intestinal stenosis. In the stomach, however, he still found the intrinsic factor (Castle). This evidence suggested that the pernicious

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anemia was caused by faulty absorption in the intestinal tract. Strauss (1934) mentioned a boy, eight years of age, who had pernicious anemia following the development of numerous short circuits between various loops of small intestine. Strauss also reported a case of pernicious anemia in which the patient was a man who was receiving an adequate diet and whose gastric juice contained the intrinsic factor. The patient, however, had pernicious anemia apparently because he was unable to absorb material necessary for formation of blood, because of multiple intestinal anastomoses.

Miller and Rhoads (1935) have produced macrocytic anemia in swine by feeding them a deficient diet. Achlorhydria, diarrhea, and changes in the bone marrow, which were characteristic of pernicious anemia, also occurred. Remissions could be produced by feeding liver extract. Unpublished work in their laboratories suggested that the lack of an intestinal secretion is not the only important factor. After resection of almost the entire ileum of dogs, the blood picture was only that of a mild hypochromic anemia. These investigators said that " apparently some disorder involving both the stomach and intestine is required to produce the desired results."

Ivy, Richter, Meyer, and Greengard (1934) observed that dogs deprived of their stomachs had a hypochromic anemia that responded to administration of iron. Brown (1934) intimated that pernicious anemia is almost invariably associated with lesions of the gastrointestinal tract.

It would seem that a number of conditions which involve the intestinal tract may, therefore, be accompanied by the blood picture of pernicious anemia.

Hartmann and Pilliet first described hypertrophic intestinal tuberculosis in 1891. The studies by Rubin (1930) indicate that gastrointestinal tuberculosis is common among patients who die of chronic pulmonary tuberculosis. Davis (1933) observed that in 22 of 29 cases of intestinal tuberculosis the involvement was at the ileocecal region. Keefer, Huang and Yang (1929) pointed out that in cases of intestinal tuberculosis the degree of hypochromic anemia was greater in cases in which diarrhea was present than it was in cases in which diarrhea did not occur. However, Brown and Sampson (1930) are among the few writers who have stated that intestinal tuberculosis might produce a blood picture suggestive of pernicious anemia. In such cases, they considered the frequently associated stricture of the small bowel as the possible etiologic factor in the production of this blood picture. No anemia, however, was reported by Masson and McIndoe (1929) or by Counseller (1929) in their cases of hyperplastic tuberculosis of the ileum.

Regional ileitis, as first described by Crohn, Ginzburg, and Oppenheimer (1932), was supposedly confined to the ileum and was usually accompanied by a moderate progressive anemia. More recently, Harris, Bell, and Brun (1933) and Homans and Hass (1933) have observed that the condition might occur at any point in the intestinal tract. Bissell (1934), Binney (1935), and Mixter (1935) did not mention anemia in their reports, but Brown, Bargen, and Weber (1934) observed a mild to a moderate secondary

anemia in 50 per cent of 18 cases of regional ileitis. A review of the literature does not reveal any cases of regional ileitis in which there was a macrocytic type of anemia.

It is well recognized that anemia may be associated with diarrheal diseases which cause little or no hemorrhage. This may, in part, be the result of a deficiency associated with the rapid flow of intestinal contents and a resulting want of absorption in the intestine. Cramer (1923) and Goldblatt and Benischek (1927) found that both vitamins A and B were necessary for the development of the healthy mucous membrane of the intestines and for maintaining its resistance to infection. Tilden and Miller (1930) observed marked changes in the colon and clinical signs of human colitis among monkeys which were fed with diets which were deficient in vitamins. Keefer, Yang and Huang (1929–1931) reported several cases in which chronic dysentery was associated with various types of anemia. The anemia varied in its severity and in its morphologic characteristics. Hyperchromic, hypochromic, macrocytic, and microcytic types of anemia were observed. Even the characteristic clinical features of pernicious anemia were present in some of these cases. In some of the cases the anemia responded to the administration of liver, iron, or a high caloric diet; in some cases the anemia improved after the patients recovered from the dysentery. These authors concluded that the syndrome of pernicious anemia can develop without changes in gastric acidity in cases in which patients have received inadequate diets and have had a pathologic process which interfered with normal nutrition.

We might mention the frequent association of the blood picture of pernicious anemia with other conditions which involve the intestinal tract but which are not considered in this study. Birkeland (1932) in his excellent study on "Bothriocephalus anemia" considered in detail the relation between Diphyllobothrium latum and pernicious anemia. Logan (1921) reported four cases in which there was infestation with Balantidium coli. All of these patients had a blood picture of pernicious anemia and, in addition, had subacute combined sclerosis. Reed and Wyckoff (1926), Baumgartner and Smith (1927), and Castle, Rhoads, Lawson and Payne (1935) have pointed out the similarity between the blood picture of sprue and that of pernicious anemia. Other workers have observed the similarity in the microscopic appearance of the intestine in sprue (Castle, Rhoads, Lawson, and Payne, 1935), intestinal infantilism (Bennett, Hunter, and Vaughan, 1932) and various types of chronic diarrhea (Linder and Harris, 1930). Wills (1934) reported a few cases of tropical macrocytic anemia in which the anemia was distinctly different from pernicious anemia and was not necessarily associated with diarrhea, defective gastric secretion, or pregnancy.

An explanation of the production of the macrocytic anemia that frequently is seen in association with lesions of the intestinal tract has been offered by Castle and his coworkers (1929, 1930, 1931). Castle, Town-

send, and Heath (1930) said: "Next to a defect of the original formative process within the stomach, the loss of the absorptive power of the intestinal tract either mechanically or by way of bacterial invasion or the destruction in the bowel of the effective principle after formation would be the most obvious ways in which a deficiency of the final effective substance could be brought out. These remarks indicate that a defect of gastric function alone is not necessarily the only way in which, quite in accord with our hypothesis of the nature of the disease, a deficiency of the necessary substance might be produced." This existence of intestinal impermeability to the hematopoietic products of gastric activity appears very plausible from the work of Gänsslen (1930). He first demonstrated the increased effectiveness of the active principle of liver when given intramuscularly instead of by mouth. This work was later confirmed by Schilling (1931). It therefore appears that the macrocytic anemia produced in certain lesions of the intestinal tract probably is the result of disturbance in either the formation or the absorption of the final effective principle. It recently has been suggested (Erös and Kunos, 1936) that hematopoietic substances are produced not only in the stomach but also in the entire intestinal tract, in other incretory organs, and in all organs containing an argentaffin cell system.

Material Examined

This paper is based on a series of 20 cases (table 1) in which anemia was associated with lesions of the ileum and colon. These cases have been studied from the standpoint of type of anemia, and the type of lesion has been verified at operation.

Table I

Conditions Found at Operation and Type of Anemia Present

Condition found	Number of cases	Macrocytosis or picture of pernicious anemia, cases	Hypochromic, microcytic anemia, cases	Hypochromic, normocytic anemia, cases
Inflammation of terminal portion of ileum	7	6	1	0
Ulcer of the ileum	4	1	1	2
Carcinoma of cecum	3	1	0	2
Fecal fistulas	2	1	1	0
Tuberculosis of ileum and cecum	2	0	2	0
Carcinoma of ileum	1	1	0	0
Diverticulosis of colon and chronic ulcerative colitis	1	1	0	0
Total	20	11	5	4

In seven cases of proved ileitis of the terminal portion of the ileum there were six instances of macrocytic anemia and in the remaining case the anemia was of the microcytic hypochromic type. Apparently, the macrocytosis was not dependent on the degree of involvement of the ileum because

the extent of involvement of the ileum was as great in the case in which microcytosis occurred as it was in the remaining six cases. Hemorrhage was not a factor as it was not present in any of the cases. The patient who had microcytic hypochromic anemia was a male, which would rule out the possibility that a primary microcytic hypochromic anemia might have been the basis for the microcytosis. One of these cases is of particular interest because a diagnosis of pernicious anemia had been made and the patient had received adequate treatment for pernicious anemia before coming to the clinic. Free hydrochloric acid was present in the gastric contents. Large doses of liver extract administered parenterally for 10 days prior to operation did not produce any change in the degree of anemia. There was no increase in the percentage of reticulated erythrocytes. At operation the patient was found to have an extensive inflammation of the lower portion of the ileum with slight obstruction. Following operation the blood picture gradually improved and within one month the number of corpuscles was normal and the erythrocytes were normal in size. During this period no treatment for the anemia was given. In the cases in which the patients survived the operation, the blood rapidly returned to normal without specific treatment. Three patients died following operation.

In the six cases in which macrocytic anemia was present, the erythrocytes were well filled with hemoglobin and closely simulated those found in cases of pernicious anemia. However, there was but little poikilocytosis as compared with the degree usually seen in pernicious anemia. The leukocyte picture as a rule showed a shift of the neutrophiles to the left and in no instance was there a shift to the right with thinning and stranding of the individual lobes of the nucleus as is so characteristically seen in cases of pernicious anemia. It thus will be seen that, in spite of a high color index, detailed study of the morphology of the blood will not show the typical features of pernicious anemia and in all such instances detailed study of the patient for a disease other than pernicious anemia should be instigated. It is possible that an individual might have pernicious anemia associated with ileitis. In such instances one would expect the anemia to persist after operation, and there most probably would be symptoms of pernicious anemia, such as glossitis, symptoms of combined sclerosis, and achlorhydria.

Four patients who had an ulcer of the ileum also had hypochromic anemia. In one of these cases the anemia was of the macrocytic hypochromic type, in two cases it was of the normocytic hypochromic type, and in the remaining case it was of the microcytic hypochromic type. In the case in which there was macrocytosis, the ulcer had produced obstruction, whereas in the other three cases there was no obstruction. The patient who had macrocytic hypochromic anemia occasionally had had tarry stools for two months previous to his registration at the clinic. At operation an ulcer was found 1½ feet (45.7 cm.) above the ileocecal valve and obstruction was present. Eight centimeters of ileum were removed. The blood returned to normal following operation and the macrocytosis disappeared.

In the other three cases there was no evidence of obstruction and no macrocytosis was found; the erythrocytes were normal in size in two of these cases and microcytic in one case. In one of the cases in which the size of the erythrocytes was normal the patient had had tarry stools for eight years prior to operation. In the case of microcytic hypochromic anemia there was no history of hemorrhage and at operation an inflammatory ulcer was found in a Meckel's diverticulum. The fact that this patient was a male would rule out the possibility of a primary microcytic anemia. In three of these cases the blood returned to normal postoperatively. One of the patients who had hypochromic normocytic anemia died shortly after operation.

In a case of obstructive carcinoma of the terminal portion of the ileum, vomiting was present and there was a macrocytic hypochromic anemia. A normocytic hypochromic anemia was present in three cases of carcinoma of the cecum; in one of these cases there was slight obstruction. The patient who had macrocytic anemia had no symptoms of pernicious anemia, although gastric analysis revealed an absence of free hydrochloric acid. Following operation the macrocytosis disappeared and the blood gradually returned to normal.

In two cases of fecal fistula one of the patients had hypochromic anemia and the other presented the typical blood picture of pernicious anemia although there was less shift of the neutrophiles to the right than there usually is in pernicious anemia. The latter patient also had glossitis, numbness and tingling of the fingers and toes, and achlorhydria. Neurologic examination revealed the presence of subacute combined sclerosis and peripheral neuritis. Following operation, the anemia persisted but responded readily to intramuscular administration of liver extract. This patient undoubtedly had a true pernicious anemia with an associated fecal fistula. This patient died a few weeks after operation. The other patient had a hypochromic anemia of the microcytic type. Operation revealed multiple fistulas which involved about 17 cm. of the ileum. The blood returned to normal within three months after operation.

Two patients who had tuberculosis of the terminal portion of the ileum and of the cecum also had a microcytic hypochromic anemia. There was no history of hemorrhage or obstruction in either case. Gastric analysis revealed an absence of free hydrochloric acid in both cases.

One patient who had diverticulosis of the left half of the colon and chronic ulcerative colitis of the right half of the colon also had a macrocytic anemia with high color index. There was no free hydrochloric acid in the gastric contents. The blood did not respond to adequate treatment for pernicious anemia but the patient recovered spontaneously two years after he left the clinic.

Comment

It is apparent that regional ileitis may produce a macrocytic anemia which apparently is independent of the amount of involvement of the ileum.

There was as much bowel diseased in one case of microcytic hypochromic anemia as there was in any of the six cases of macrocytic anemia. Hemorrhage was not a factor in this series of cases. There apparently is some abnormality of absorption and a situation possibly is produced in which there is improper utilization of the effective fraction by the liver, for in this group of cases no change in the blood picture was noted after parenteral administration of liver fractions that are effective in the treatment of pernicious anemia. In the two cases of tuberculous involvement of the ileum there was no macrocytic anemia, which may indicate that in such processes there is no abnormality of formation or absorption of the hematopoietic principle. Any lesion of the bowel that produces obstruction may so interfere with the absorption or utilization of the hematopoietic principle that a macrocytic anemia will result. Only one case of diverticulosis of the colon and chronic ulcerative colitis was studied and in this case there was a macrocytic anemia. There was no history of obstruction. The macrocytosis disappeared spontaneously.

TABLE II

Cases of Hypochromic Anemia

Case	Chief complaint	Condition found	Blood picture previous to operation
1	Diarrhea of several months' duration	Extensive inflammation of lower portion of ileum and slight obstruction	Hypochromic, microcytic anemia*
2	Fecal fistula that followed appendectomy two months previously	Multiple fecal fistulas in ileum	Hypochromic, microcytic anemia
3	Intermittent abdominal cramps over entire abdomen for 10 years	Tuberculosis of terminal two feet of ileum and of cecum, with slight obstruction	Hypochromic, microcytic anemia
4	Intermittent cramps in left upper quadrant of abdomen for two years	Tuberculosis of terminal two feet of ileum and of cecum	Hypochromic, microcytic anemia
5	Intermittent cramping pains across midabdomen for 18 months	Simple solitary ulcer of ileum, 2 cm. in diameter	Hypochromic, normocytic anemia*
6	Tarry and bloody stools intermittently for eight years	Inflammatory annular ulcer of ileum, involving 10 cm. of ileum	Hypochromic, normocytic anemia
7	Intermittent abdominal cramping pains for three years	Angulated loop of ileum with Meckel's diverticulum which contained an inflammatory ulcer	Hypochromic, microcytic anemia
8	Intermittent cramping pains in left lower quadrant of abdomen for two months	Perforating carcinoma of cecum with involvement of 10 cm. of ileum	Hypochromic, normocytic anemia
9	Colicky pains in right lower quadrant of abdomen and diarrhea of six months' duration	Cecal carcinoma (grade 2) with partial obstruction of lower portion of ileum	Hypochromic, normocytic anemia

* Patient died following operation.

If macrocytic anemia is attributable only to failure of absorption of the effective hematopoietic principle, the anemia should respond to effective liver fractions administered parenterally, but this did not occur in two cases in which the patients were adequately treated. It would appear that in regional ileitis particularly, the process in some manner produces some change, perhaps in the form of a toxin, which prevents utilization of the hematopoietic principle by the liver. Since in most instances, as has been previously stated,

TABLE III

Cases with Blood Picture of Pernicious Anemia or Macrocytosis

Case	Chief complaint	Condition found	Blood picture previous to operation
1	Intermittent cramping abdominal pains for eight years	Inflammation of terminal portion of ileum and dilated loops of intestine	Macrocytosis
2	Dull, intermittent abdominal cramps for three years	Distal 25 to 30 cm. of ileum involved in inflammatory reaction	Macrocytosis*
3	Constipation for 20 years	Regional ileitis	Macrocytosis*
4	Intermittent low cramping abdominal pain for five years	Inflammation of terminal portion of ileum, with some dilatation and obstruction	Macrocytic, hypochromic anemia
5	Numbness and tingling of hands and feet; pain in right lower quadrant of abdomen; diarrhea for three months	Inflammatory lesion involving cecum and 8 cm. of ileum	Macrocytic, hypochromic anemia
6	Cramping, intermittent pains in right lower quadrant of abdomen for two years. Condition diagnosed as pernicious anemia and patient treated with liver before admission	Extensive inflammation of lower portion of ileum with slight obstruction	Pernicious anemia
7	Cramping pain in right lower abdominal quadrant with vomiting for two months	Carcinoma of terminal portion of ileum with obstruction	Macrocytosis
8	Recurrent numbness and tingling of the feet and hands for nine years; constant dull aching pain in right upper quadrant of abdomen for one month	Diverticulosis of the left half of colon and chronic ulcerative colitis of the right half of colon	Macrocytosis
9	Anemia and weakness for one year	Carcinoma (grade 2) of cecum	Slight macrocytosis suggestive of pernicious anemia
10	Intermittent abdominal cramps for four years and severe cramping pain in lower part of abdomen for seven months	Subacute ulcer of ileum with partial obstruction	Macrocytosis
11	Numbness and tingling of hands and feet with sore tongue for eight weeks; fecal fistula for 12 years; diarrhea for one year	Multiple fecal fistula of the small intestine	Pernicious anemia*

* Patient died following operation.

the blood picture can be distinguished from that seen in pernicious anemia, the finding suggests that factors other than failure of absorption and utilization of the hematopoietic principle may produce a macrocytic type of anemia.

Since the macrocytosis and anemia disappeared following operation in this series of cases, it would not seem essential to treat such an anemia with materials effective in the treatment of pernicious anemia. It seems to us, however, that for good therapeusis such preparations should be used and preferably by the parenteral method as this should result in a rapid response of the blood to normal. One should have constantly in mind the possible coexistence of pernicious anemia, and in cases in which the clinical findings support a diagnosis of pernicious anemia, the treatment must be continued after operative procedures.

The most outstanding symptom in this series of cases was cramping abdominal pain (tables 2 and 3). We wish to emphasize that this symptom, particularly in the presence of macrocytic anemia without symptoms of pernicious anemia, strongly suggests a lesion of the ileum.

It also should be emphasized that macrocytic anemia does not always mean pernicious anemia or sprue, but in such cases patients should be studied in detail to eliminate lesions of the small intestine or liver. This is especially true if the patient presents none of the symptoms of pernicious anemia.

Summary

Macrocytic anemia frequently affects individuals who are suffering from regional ileitis. Any intestinal lesion which produces obstruction may produce a macrocytic anemia. Carcinoma of the cecum, tuberculous ileitis, and fecal fistulas did not produce a macrocytic anemia.

Parenteral administration of liver was not effective in the treatment of the anemia associated with regional ileitis. The condition of the blood improved spontaneously following operation. Coexistence of pernicious anemia and lesions of the intestine has been considered.

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MEDICO-DENTAL RELATIONS; THE DENTIST'S VIEWPOINT *

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The question of medico-dental relations is one which has been discussed for many years. It was originally prompted by the empirical findings of those early practitioners who had observed either a favorable response to the elimination of certain oral conditions, or the damaging effects of faulty dental technology. The case reports of Benjamin Rush and his contemporaries on the benefits frequently accompanying the elimination of oral infections are well known. The period in which these early practitioners lived did not offer such opportunities for investigation as exist today, yet their frequent reports on medico-dental relations are not without value.

The first school of dentistry was founded (1840) with full recognition of the existence and value of the then known medico-dental relations. The objectives of the school according to one of its founders, Chapin A. Harris, M.D.,[1] is "to give those who receive its instructions a thorough medico-dental education, so that when they enter upon the active duties of the profession they may be enabled to practice it, not alone as a mere mechanical art, but upon sound scientific principles, as a regular branch of medicine." Dr. Thomas Bond, one of the faculty of the first school, states in the introduction to his Practical Treatise on Dental Medicine[2] that "the purpose of the present work is to present to the reader a digest of information prepared with particular reference to the morbid connections certainly existing between the teeth and the rest of the body."

The handicaps imposed by the continued existence of apprenticeship methods, the rise of commercialism in many dental schools, inhibited the attainment of the health service objectives of the early schools, and dentistry for the most part continued to limit its activities to dental technology. Medicine, busy creating and utilizing new knowledge in its field, also left untouched areas now recognized as having medico-dental relations. It was not until the early part of the twentieth century that the findings of Hunter, Billings and others stimulated interest and further investigation into the possible relations which oral infections may have as etiologic factors in systemic disease. Though early interest and enthusiasm on the subject were accompanied by many misinterpretations which have led to radical and fanatic therapy, that period fortunately is about ended, and an era characterized by conservative, though progressive, attitudes has now begun.

The modern concept of medico-dental relations includes, in so far as

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we have been able to determine, several general phases: namely, the effects which oral diseases or disorders may have as etiologic factors in systemic disease; in the aggravation of already existing conditions; in the establishment of a negative phase of body defense factors; as the cause of certain reflex disturbances; and finally, the changes in the oral hard and soft tissues due to systemic disease or metabolic disorder. Obviously there is in each phase the same difficulty in establishing absolute proof that exists in connection with the etiology of many diseases.

McNevin and Vaughan,[3] in a discussion of focal infection, state that (1) "Even if absolute proof of the existence of oral and other foci of infection cannot be submitted, it is nevertheless a reasonable assumption"; that (2) "The strong circumstantial evidence advanced, strengthens the assumption"; and (3) "The exact nature, however, of the effect which oral foci exert on the body, in each case cannot always be determined." From the viewpoint of the dentist, it is not any spectacular nature or effect of oral foci which should cause them to command attention, but rather the great frequency with which they occur. It is one thing to attach little importance to a single oral lesion, but quite another to disregard the probable effects of many carious teeth, or multiple supporting tissue lesions, in the mouth of one patient. It is the rare individual today who does not harbor either one important or several minor foci. Clinical search for spectacular or potent oral foci often overshadows consideration of the long range effects of those of apparently lesser and more immediate import. If it be true that most diseases are due to a combination of forces, may it not be said that apparently harmless multiple foci constitute a force, which though it may not be the most active, is nevertheless a needless burden to the individual? Perhaps we dwell too heavily on this point; however, it is prompted by the appallingly high incidence of mouth filth, dental caries, and so-called pyorrhea among American people. One has but to examine several thousand adults or children to reach the conclusion that a large number are carrying multiple oral foci which should be eliminated.

Much has been written regarding the routes by which the products of oral sepsis may be transported to other parts. For the most part, emphasis on the spread of infection by the blood and lymph stream has excluded consideration of the probable effects of transfer by swallowing, aspiration, or by continuity of tissue. Because of the location of oral infections and the great frequency with which they occur, should not these avenues for the spread of septic products be rated higher in importance than they now are? Even though the transfer of infection by continuity of tissue, aspiration or swallowing be regarded as devoid of significance in the etiology of respiratory or gastrointestinal diseases, may it not impose aggravating factors which make successful treatment difficult? In view of the widespread lack of mouth hygiene, the high incidence of dental caries and pyorrhea, it is not illogical to assume that effective mouth hygiene offers some protection against certain respiratory or gastrointestinal diseases.

The physician should have knowledge of all of the oral disease or disorders of his patient; therefore, the report of the dentist should be a comprehensive one, going far beyond the now too common, and too limited statement as to the patient's oral condition. These reports, I believe, should include data relative to conditions which may bear causal relations to systemic disease. There are good reasons for the assumption that there should be included information as to the extent of dental caries, pulpless teeth, infections of the peridental tissues, alveolar abscesses, residual infection, impacted teeth, mouth filth, and marked malocclusion.

Dental caries, the most frequently occurring physical defect among civilized peoples, has for years been regarded as a condition to be treated from a point of tooth conservation. From research findings and clinical observation one is led to conclude that dental caries, especially in youth, may be regarded as an important focus of infection. It has been shown by Noyes, Fish and others that fluids may easily be passed through the tubules of the dentin to the pulp. Hartzell and Henrici [4] state that, " Our results confirm in a general way the studies of Collins and Lyne. If our observations are correct we must conclude that in approximately one-half of the number of teeth invaded by caries or surrounded by pyorrhea, the pulps are already infected by streptococci." In 1920 these investigators state that subsequent studies give " ample confirmation of the opinion previously arrived at from bacteriological studies that the pulp may be (*a*) invaded by microörganisms long before it is actually exposed by caries, and (*b*) may be repeatedly injured by microörganisms long before it actually undergoes necrosis." Thoma [5] has shown that the *Streptococcus viridans* is the most important factor in pulp infection. He states that in 16 out of 21 cases with closed pulp chambers, pure cultures of *Streptococcus viridans* were produced, and concludes that " an infected vital pulp, no matter whether there are marked periapical changes or not, is often a very important focus of infection."

The evidences of favorable response to the treatment of dental caries is too frequent to put to one side as being without significance. The elimination of lymphadenitis, and the increase in alertness and in general well-being have been observed many times in this country and abroad. While there are involved such other factors as the relief of pain and more effective mastication, we believe that treatment which stops the transfer of septic products through the tubules of the dentin to the pulp under biting stress or perhaps without it, is in the main responsible.

The oral focus about which more has been written than any other is the chronic alveolar infection. Presenting as it does a closed focus, there is much to prove that it is a common etiologic factor in diseases of adjacent and remote structures. It would be out of place here to enumerate the list of specific conditions commonly ascribed to these foci. It should be said, however, that it is all too common practice to consider chronic alveolar abscesses as the only oral source of focal infection. There is no sound basis for the apparent exclusion of other foci which may also be present. Neither

are there any grounds for the optimism so frequently encountered in the absence of gross radiographic evidence. Any estimate of the effects of these infections as judged by radiographic evidence is obviously unreliable. It has not yet been shown that pulpless teeth can be successfully treated, and until this proof is at hand, protection of the patient should warrant their removal. Statements that the extraction of such teeth is not always followed by a favorable response are somewhat beyond the point. Dental infections may not have been a cause of the disease under consideration; however, they should be rated as potentially dangerous and therefore eliminated.

As to the condition commonly called pyorrhea, there appears to be much confusion as to the part which it may play in systemic infection. Much of the confusion results from the fact that all too frequently all changes in the supporting tissues of the teeth are included under the term pyorrhea. Atrophic changes, so-called recession, of the alveolar and peridental tissues are unimportant as etiologic factors in focal infection; however, because these atrophic changes are often accompanied by increased mobility of the teeth, a focus of infection is often assumed to exist and extraction of the teeth is advised. It is the peridental infection, or the suppurating pyorrhea pocket, which should command the interest of the physician. The tissues involved in this condition, abundantly supplied as they are with lymphatic and capillary blood vessels, offer many avenues for the extension of bacteria and their products. The disease should be regarded as a focus of infection of considerable importance, not only because it affords opportunities for metastasis, but also for the reason that drainage from the suppurating tissues tends to raise the oral bacterial count to a high point. The accompanying increase in mouth bacteria, though usually disregarded, may in chronic suppurating infection of the alveoli and peridental tissues establish by a spread of infection through aspiration, continuity of tissue, or swallowing, relations to diseases of the gastrointestinal, and upper and lower respiratory tract. Whether or not one accepts mouth bacteria as bearing causal relations to these diseases, it appears that in their treatment at least, the establishment and maintenance of mouth hygiene should be good routine practice.

Yet another common oral source of infection is seen in the residual areas remaining in the soft tissue of alveolar bone following the removal of teeth. They are caused by leaving infected root apices, cysts, foreign bodies, loose particles of alveolar bone, or by the incomplete removal of pathologic tissue. These residual areas are so frequently found in the partially or completely edentulous jaw, that the absence of teeth still leaves ground for suspicion that such areas may exist. It is also good routine practice to suspect the presence of unerupted teeth in the edentulous jaw. The patient is not usually conscious of the presence of residual areas, unless symptoms of acute infection arise; therefore, for practical diagnostic purposes absence of local symptoms does not warrant the assumption that these areas do not exist and bear some relation to diseases of adjacent or remote tissues.

In addition to oral infections and their possible relations to systemic disease, the reflex disturbance frequently established by unerupted and impacted teeth, pulp stones and sclerotic bone are of interest. The removal of these occasional causes of reflex disturbance have so often brought relief, that they should be of considerable import in oral diagnosis.

In considering oral infections in their relation to systemic disease, it is frequently stated that individuals may carry most of them without apparent harm. However, one must conclude that the body defense factors are not inexhaustible, and even though one held that oral infections are devoid of direct causal relations in systemic disease, it would be difficult to justify a premise which held that they did not constitute a needless burden which tended to jeopardize the defensive powers of the individual. In persons who have lost much of their normal defense, the coexistence of chronic oral infections with systemic disease is too frequent to be overlooked.

It is interesting to note the views of Haden,[6] who states that: "In studying patients with systemic disease of focal origin, all possible foci of infection should have careful clinical consideration. Every student of focal infection is impressed with the fact that no subject in medicine must be handled with more mature clinical judgment when one sees the harmful results of the reckless removal of teeth, the frequent ascribing of conditions to focal infection when due to entirely different causes, and careless promises for the relief of systemic lesions by the extraction of teeth. Careful study of the subject must convince one of the importance of dental focal infection in the causation of systemic disease."

Pemberton,[7] in speaking of the removal of focal infection in arthritis, makes an excellent point when he states that "Much emphasis will be placed here upon the removal of focal infection, but the importance of a medical understanding of the individual as a whole precedes this. Notwithstanding the theoretical propriety of removing infections, any step in this direction may, especially in the later stages, be not only unprofitable but dangerous." This statement is especially applicable to the removal of oral infections. Very frequently when systemic disease demands the removal of these infections, the extraction of a number of teeth at one period is followed by severe reactions and exacerbation of the patient's symptoms. In the terminal diseases, the gradual elimination of oral infections, sometimes over a period of weeks appears to be good practice.

Another side of the question of medico-dental relations includes those points at which the dentist should refer his patient to the physician. In general this is indicated when (*a*) it is thought that systemic conditions are etiologic factors in the establishment and maintenance of certain oral diseases, disorders or deficiencies, and (*b*) when oral manifestations of systemic disease, for which the patient is not being treated, are recognized by the dentist. To the end that graduates in dentistry shall be more capable of initiating intelligent action on these two points, American dental education has made important changes in its curriculum and objectives.

As yet the exciting cause of dental caries is unknown, therefore preventive measures are for the most part empirical. There appears, however, to be general recognition of the value of high structural resistance to dental caries, and to the protection afforded by harmonious and adequate development of jaws and teeth. Inasmuch as tooth development begins in intrauterine life, and as the follicles of both the deciduous and permanent teeth are developed at birth, one may well say that the problem of satisfactory development, and the prevention of dental caries in part at least, up to the eruption of the first tooth, is one for the physician. It is well known that up to this point many things may happen to prevent harmonious development. Over these disturbing factors, the dentist has no control. Therefore, the physician must in the main be responsible for the inauguration of such preventive or therapeutic measures as may be necessary.

It is difficult to agree with those who approach the problem of arresting or preventing dental caries through dietary measures alone. The simple administration of calcium or phosphorus compounds and vitamin bearing substances guarantees little, unless it can be shown that dietary deficiencies actually exist. Medical understanding of the patient as a whole is necessary for the reason that many factors may prohibit assimilation and fixation of inorganic salts. The patient may be suffering from some systemic disease or metabolic disorder or may be eliminating desirable inorganic salts too rapidly. Diagnosis by the physician should be the basis for judgment in the matter of diet as a preventive measure in dental caries. The physician and the dentist, coöperating in arresting or preventing this widespread condition, can accomplish much more than can either one alone.

The frequent need for coöperation of the internist is evident in the prevention and treatment of supporting changes (pyorrhea) when one considers the constitutional factors usually involved. These changes seldom occur before middle age, and are rarely established in a marked way so long as the patient has sufficient resistance to withstand the burdens imposed by such local factors as malocclusion, faulty restorative work, or inadequate mouth hygiene. Obviously certain changes can be accounted for in terms of advancing age; however, both acute and chronic systemic disorders usually leave their mark on the alveolar and peridental tissues and in addition lower their resistance to infectious and mechanical stresses. These oral manifestations of metabolic disturbances present a much wider field than is ordinarily thought. They include such conditions as diabetes which, in addition to lowering resistance, may be accompanied by changes in the oral mucous membrane; anemias, with their frequent oral symptoms; malnutrition with its accompanying deficiencies; nephritis and many other conditions which obviously need not be considered here. It is sufficient to repeat that such conditions play no small part in disturbing the health of the alveolar and peridental tissues. Most human dentures are so poorly developed, or become so damaged through caries, that harmonious function of the denture is impossible. Factors of ill health imposed on existing disharmonies often

bring about complete edentulation in early middle life. The search for a single local etiologic factor in supporting tissue changes, or the attempt to prevent or successfully treat these conditions as purely local changes, is for the most part futile. Diagnosis and treatment by the internist in a large number of cases is either a prerequisite to or accompaniment of successful dental service in preventing or treating these conditions.

The illustrations which have been drawn serve only to show examples of areas having medico-dental relations. In the past these areas have been relatively untouched by either medicine or dentistry. Dentistry, largely because of certain heritages which it had difficulty in overcoming, centered its efforts for the most part on restorative and replacement procedures. As research and clinical observation caused revival of interest in the relation of oral sepsis to systemic disease, changes in attitude began to take place. The key to the solution of the problem, dental education, was stimulated by an excellent report on dental education by the Carnegie Foundation. Among other things this report held that dentistry "properly a form of health service," expanded as it should be in biological scope and strengthened in its health service aspects, would be devoted, "to detection and provisional diagnosis of dental and oral symptoms that indicate the prevalence or imply the probable existence of ill health elsewhere in the body and to suitable, supplemental, advisory health service including consultation with the patient's physician, based on such observation and diagnosis."

Following a four year curriculum study in which medico-dental relations played an important part, the American Association of Dental Schools adopted among other objectives of dental education, those which call for the education of students in order that they may be (*a*) competent in the maintenance of oral health, and in the treatment of oral diseases, disorders and deficiencies with understanding and appreciation of the relationships between oral and systemic conditions in health and disease, and (*b*) be able to coöperate effectively with persons engaged in allied fields of service. Recommendations relative to a suggested curriculum leading to attainment of these objectives were also adopted by the Association.

There is sound basis for anticipating that research and clinical observations will show even more important and more extensive medico-dental relations than are now thought to exist. Utilization of knowledge in the areas which have so long been neglected depends primarily on education and coöperation. Dental education is taking many forward steps and by 1937 nearly all dental schools will require two years' pre-dental work for admission to improved four year courses. Dental organizations are becoming increasingly more active in the promotion of research in the biological phases of dentistry. In general, trends indicate a healthy forward movement to new goals and to the acceptance of broader responsibilities in the health service field.

In closing, may I express appreciation for the coöperative spirit with which medicine has approached problems involving medico-dental relation-

ships. It has been both helpful and encouraging. Continued and extended coöperation between the two professions will, I am certain, mean much to the patient, the physician, and the dentist.

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CASE REPORTS

ACUTE GUMMATOUS MYOCARDITIS SIMULATING ACUTE MYOCARDIAL INFARCTION *

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Coronary thrombosis was rarely diagnosed ante mortem prior to 1918. At that time textbooks on medicine contained no reference to the clinical condition. It is a tribute to American medicine that the clinical recognition of cardiac infarction is due to the observations and studies of American physicians.

Osler [1] was familiar with the condition. Dock [2] was one of the first to describe a case which had been diagnosed ante mortem. However, its significance was not appreciated until Herrick in 1912 [3] and again in 1918 [4] had described its clinical features and drawn attention to the fact that it could be easily diagnosed and that many cases recovered.

The importance of the subject soon became quite apparent, so that within a comparatively short time it was more frequently recognized and diagnosed, at first, as is usual, in places where teaching was done. The transition in the state of our knowledge of the condition was ably expressed by Christian [5] in 1925: "Twenty-five years ago, cardiac infarction as a result of coronary thrombosis had been shown to me in the postmortem room but I recall no reference to cardiac infarction or, as it is sometimes termed, coronary thrombosis, as a condition to be recognized during life. My teachers of that day seemed unable to make the diagnosis in the clinic. Today I find that fourth year medical students in my wards at the Peter Bent Brigham Hospital consider it in rendering a diagnosis on a patient assigned to them for history and physical examination, and adopt or eliminate it with a very considerable degree of accuracy. In other words, the students of today diagnose with much accuracy a condition that was hardly known to medical students twenty-five years ago."

The older practicing physicians were naturally slower to appreciate the condition. However, with increasing knowledge, they too have become familiar with it, so that today coronary thrombosis is frequently and usually correctly diagnosed by the practicing physician. Hamman [6] expresses very well the change which has occurred. " Ten years ago I was often called to see patients with symptoms of collapse following a severe attack of pain in the chest, and under these circumstances had the satisfaction of pointing out how simply the diagnosis of coronary thrombosis could be made. Today the humblest practitioner of medicine is so familiar with the clinical picture and so alive to its recognition that the opinion of the consultant is seldom needed to suggest the diagnosis. Now when almost every sudden pain in the chest of a person past middle life is called coronary occlusion, it seems appropriate to sound a warning. There are other diseases of the heart, lungs, and abdominal organs which so closely

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resemble coronary occlusion that they are often distinguishable from it only with great difficulty and sometimes not until autopsy discloses in detail the real state of affairs."

This coincides with my experience. Paradoxically, the consultant no longer introduces the diagnosis of myocardial infarction, but now either confirms it or diagnoses one of the less common but equally important conditions simulating myocardial infarction.

Naturally, at first mistakes in diagnosis occurred because the clinical condition was not clearly understood. One of the errors was to diagnose an acute surgical condition in the abdomen because of the prominence of the abdominal symptoms, and in several instances exploration of the abdomen was done and no pathology found. Later the correct diagnosis was shown at autopsy. Levine and Tranter [7] and later others, Hamburger,[8] Hardt,[9] Anderson,[10] Coffen and Rush,[11] Portis,[12] directed attention to this phase of the problem.

Now the situation is reversed. Failure to recognize myocardial infarction rarely occurs. In fact, it is sometimes erroneously diagnosed in the presence of conditions which resemble it. The error may prove serious or even fatal to the patient, especially if the condition is one which could have been relieved by proper medical or surgical procedures. Within the past few years the literature on this subject has contained reports of various conditions which simulate myocardial infarction. Among these are acute pericarditis,[6, 29] pulmonary embolism,[6, 15, 16, 17, 29] acute upper abdominal disease,[6, 8, 19, 20, 21, 29] interstitial emphysema,[6] ruptured aorta,[6, 26, 27] dissecting aneurysm of the aorta,[22, 23] ruptured auricle,[28] spontaneous pneumothorax,[29] sudden change in the rhythm of the heart.[30, 31]

I have seen examples of many of these; and I have also seen in consultation and on the wards of the University Hospital instances where coronary thrombosis was diagnosed, and the condition later shown to be acute mediastinitis, severe hemorrhage from a duodenal ulcer, acute acidosis associated with diabetes.

It is the purpose of this communication to draw attention to still another condition which presents a confusing resemblance to coronary thrombosis. A patient was observed on the wards of the University Hospital with the symptoms, physical signs, blood pressure readings, laboratory findings, electrocardiographic evidence and clinical course usually considered characteristic of acute myocardial infarction. This similarity justifies the presentation of the details of the case.

Case Report

A white male, truck driver, aged 26 years, was admitted to the University Hospital July 6, 1932, acutely ill, complaining of constriction beneath the lower end of the sternum and the upper abdomen and nausea and vomiting of three days' duration. The family history was unimportant. The patient had been married seven years; his wife and one child five years of age were living. Three years ago his wife had a miscarriage at the third month of pregnancy the cause of which was undetermined. Prior to the past year he was employed as a truck driver for a lumber and trucking company and since that time he had done odd jobs as a laborer. During childhood he had measles, mumps, pertussis and scarlet fever. There was no history of diphtheria, pneumonia or rheumatic fever. Seven years before admission he had had a chancre and a gonorrheal infection; two years later he had a generalized body eruption which had reappeared three months prior to admission. Because of the recurrence of the

rash and a four plus Wassermann reaction, he was given a series of intravenous and intramuscular injections. This therapy was discontinued two weeks before admission because of the appearance of a dry, scaly dermatitis upon the hands and the face. His wife, who had also been receiving treatments for syphilis, was then a patient in the University Hospital dangerously ill with a severe form of dermatitis exfoliativa resulting from arsenical medication.

The present illness began on July 3, 1932, three days before admission, with pain and constriction in the lower chest and upper abdomen, nausea, and vomiting. The symptoms persisted and were associated with a non-productive cough, generalized soreness throughout the body, extreme weakness and exhaustion, and severe pain in the lower lumbar region that was aggravated by motion.

The physical examination showed the patient to be acutely ill, in shock, dyspneic, complaining bitterly of a sense of constriction in his chest. The skin revealed a rash with scaly, psoriasis-like lesions located on the abdomen, the arms, and the legs; and also many macules and papules, particularly prominent on the palms of the hands and the soles of the feet. The tongue was red and dry. The oral hygiene was poor and the teeth were decayed. There was no general adenopathy. The veins of the neck were not prominent. The examination of the lungs failed to reveal abnormal findings. The apex beat of the heart could be neither seen nor felt, nc cardiac enlargement could be found, and the heart sounds were of faint intensity. The apex rate was 100 beats per minute with regular rhythm. The radial pulse was very feeble and could scarcely be detected. The blood pressure reading was 106 systolic and 80 diastolic. The superficial and deep reflexes were absent. The edges of the spleen and liver were not palpated. There was no pitting edema of the extremities. The temperature on admission was 98 degrees. The following day the temperature was found to be 102.8°, pulse 100, respiration 20. The blood count was as follows: Hemoglobin 89 per cent; red blood cells 5,200,000; white blood cells 23,300; polymorphonuclears 87 per cent; lymphocytes 13 per cent. The examination of the urine showed two plus albumin with numerous hyalin and granular casts. There was an elevated non-protein nitrogen (66.6 milligrams per cent) and a blood sugar of 129 milligrams per cent. The electrocardiogram showed a high take-off of the T-wave in Lead I, with an abnormal take-off of the T-wave in Lead III, having the pattern usually seen in acute myocardial infarction. At this time the heart sounds were less intense, gallop rhythm was present, and moisture appeared in the lungs posteriorly.

The dermatological service reported: "This patient shows a condition suggesting psoriasis by the color, distribution and grouping of the lesions on the abdomen, chest and legs; however, it may possibly be a papulo-squamous syphilitic or arsenical dermatitis."

During the 14 days that he was in the hospital, he continued to have an elevated temperature (figure 1), an increased pulse rate and a persistent leukocytosis. The sedimentation time of the blood was 1 hour and 12 minutes; the blood non-protein nitrogen level varied from 66.6 milligrams per cent to 198 milligrams per cent. The blood Wassermann on admission was reported as showing partial fixation with both antigens, while the second Wassermann reaction was reported as negative. The Wassermann reaction on the spinal fluid was also negative. Electrocardiograms were made every two days and showed consecutive changes (figure 2). The heart sounds continued to vary in intensity with definite gallop rhythm. The blood pressure gradually dropped to 90 systolic and 60 diastolic, signs of circulatory failure increased, and 14 days after admission he expired.

A partial autopsy was performed at the University Hospital July 20, 1932, by Dr. R. B. Hartsfield of the Department of Pathology. "The examination of the peritoneal cavity was negative with the exception of the enlargement of the mesenteric

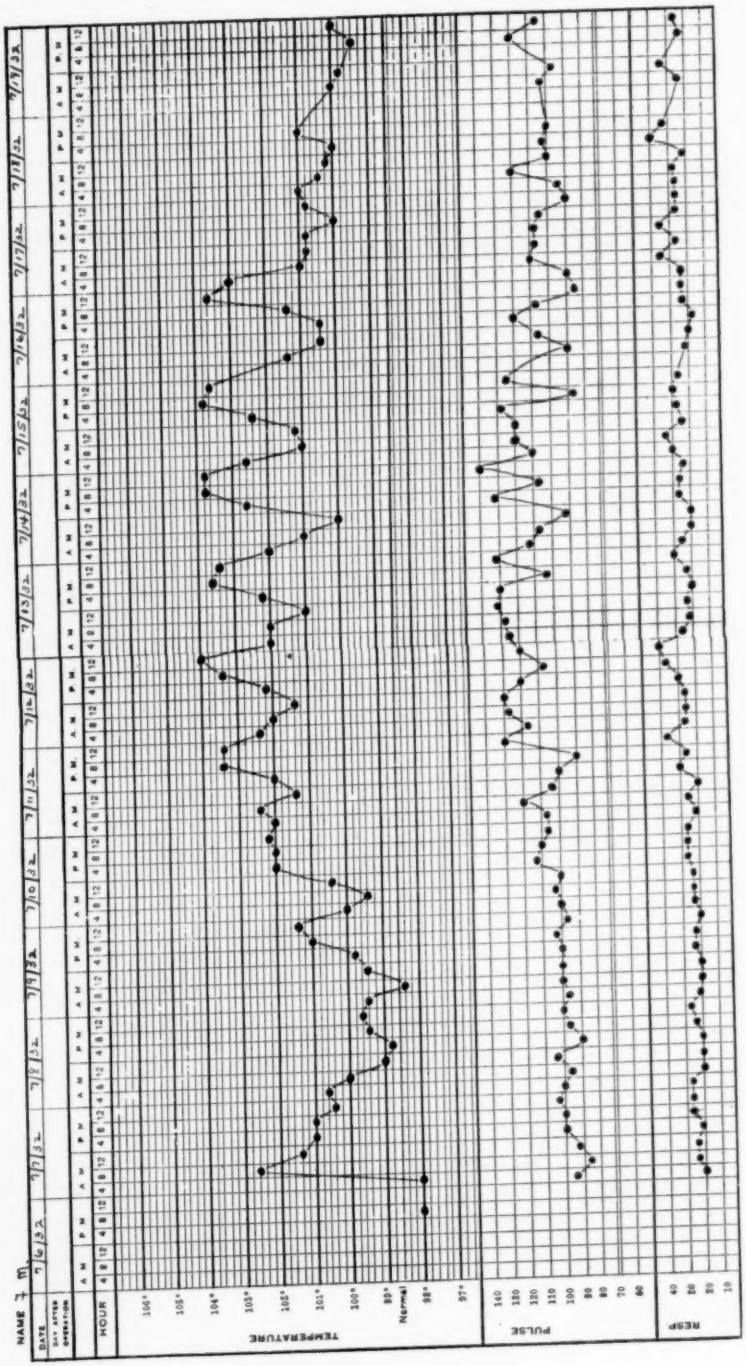
NAME
DATE
Date after operation
HOUR
TEMPERATURE
PULSE
RESP.
Normal

FIG. 1.

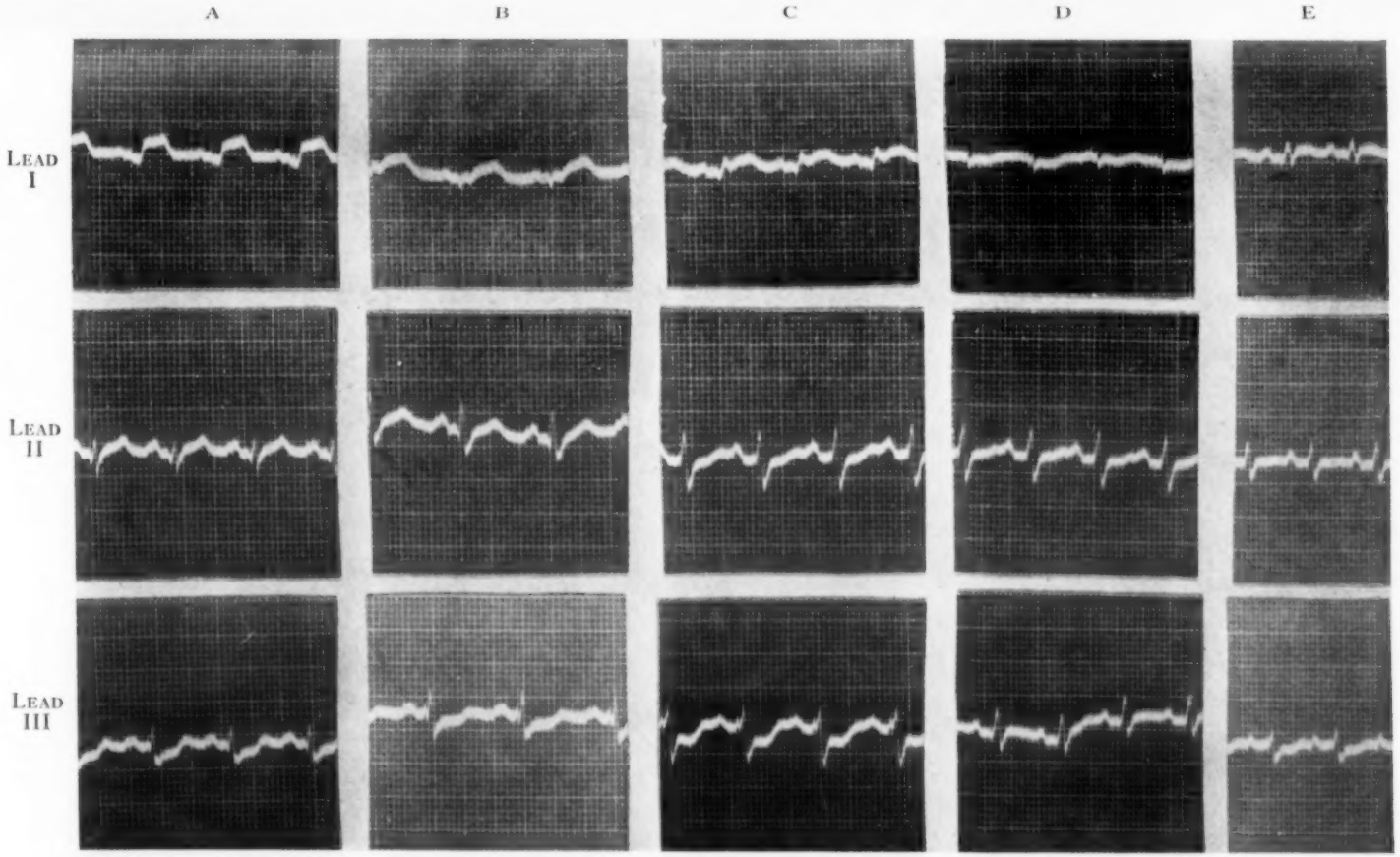

FIG. 2. *A*—Electrocardiogram taken four days after onset. *B, C, D, E*—Taken at two day intervals. Note successive changes in the R–S–T complexes in Leads I and III.

lymph nodes. Both pleural cavities contained 100 c.c. of slightly blood tinged fluid. The pericardial cavity was without evident lesion. The heart was found to be somewhat larger than usual and on the exterior surface showed a few milk patches. The aortic valve showed some thickening along the line of closure. The area of the aorta attached to the heart was considerably thickened and showed pearly gray elevations. The other vessels showed nothing unusual. The endocardium was somewhat lighter in color than usual. The myocardium was lighter in color than usual and there were areas scattered throughout having a reddish streaked appearance. This was notably marked in the left ventricle. The coronary arteries showed a moderate amount of yellowish thickening; however, no areas of occlusion and no thrombus were found. The external surface of the lungs was reddish in color and scattered over the surface of both lungs there were found slightly elevated reddish areas ranging from 1 cm. to 3 cm. in diameter. On section these areas extended down into the lungs and were fairly well demarcated, considerably reddish in color and firmer than the surrounding tissue. The remainder of the lung tissue was crepitant throughout. The spleen was without evident lesion. The liver margins were somewhat rounded; on section the cut surface was mottled yellowish and brownish in color. The kidneys showed nothing unusual on external examination. On section one small area on the right and two small areas on the left were found that were gray in color and slightly demarcated with a slightly hemorrhagic edge. The remainder of the kidney section was not remarkable. The capsules stripped with slight difficulty leaving a smooth surface. The aorta showed marked thickening and some calcification of the thoracic portion. The area above the celiac axis showed similar thickening. Mingled with the yellowish elevations were pearly gray elevations which appeared to be the pre-

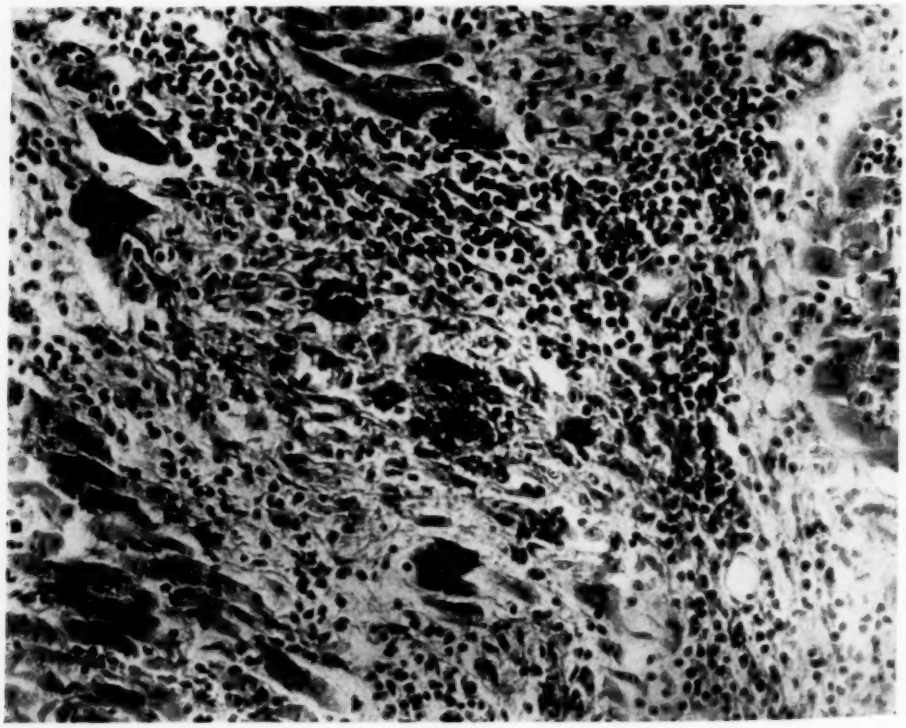

FIG. 3. Heart muscle. Area of necrosis showing giant cells in mononuclear reaction.

dominating lesion. There was considerable longitudinal wrinkling of the intima. This was most marked in the arch of the aorta which appeared to be slightly dilated." The anatomical diagnosis was: syphilitic aortitis, apparent acute myocarditis, multiple infarction of the kidney, multiple infarction of the lungs. "The microscopic examination of the aorta revealed lesions typical of syphilitic aortitis. Examination of the heart muscle showed giant cells in areas showing mononuclear reaction (figure 3). The examination of the aorta and the heart muscle for spirochetes was negative."

Discussion

The symptoms, physical signs, leukocytosis, elevated temperature, increased sedimentation time, and repeated abnormal electrocardiograms warranted a diagnosis of myocardial infarction due to coronary thrombosis, but in an attempt to associate this condition with syphilis, one encountered certain difficulties. It is generally agreed by most writers that syphilis is rarely the cause of coronary thrombosis. Levine [32] stated that 4.5 per cent of his cases of coronary thrombosis were syphilitic and that it would not follow that even in these syphilis had a direct causative influence in the coronary thrombosis. That it was so of the patient, aged 36, who was the youngest of his series, seemed likely.

Syphilis is supposed to affect the myocardium in the following ways: (1) Specific fibrous myocarditis of Warthin; (2) Gummatous myocarditis; (3) Involvement of the coronaries either at the ostium or by producing an endarteritis. In our patient, although it was evident that the myocardium was damaged, syphilitic myocarditis did not seem to be the logical diagnosis because the existence of the specific fibrous form has not been definitely proved and because of the rarity of the gummatous type. Pathological studies by Scott,[33] Clawson and Bell,[34] Martland,[35] and Saphir [36] would indicate that there is no specific form of myocarditis due to syphilis, notwithstanding the observations made by Warthin.[37] The pathologist has been unable to differentiate the fibrous changes found in the myocardium in known syphilis from the fibrous changes found in other conditions including arteriosclerosis. This fact and the failure to find spirochetes in the myocardium have been used as evidence against Warthin's [37] concept that a specific form of myocarditis is found in syphilis. MacCallum [38] states that it is fairly self evident that syphilitic disease of the myocardium could occur in the form described by Warthin; and that it could heal with the traces indicated by such scars is equally clear, but he has seen very few cases in which active syphilitic myocarditis was suggested and has been unable to feel sure that the scars found in the myocardium were really syphilitic. Warthin's views have been supported in some instances by Boyd,[39] Wilson,[40] Paullin,[41] and Hamman and Rich.[42] The majority agree, however, that it is a rare condition if it exists at all. It might be well to direct attention to the difficulties which Welch,[43] Doehle,[44] and Heller [45] encountered when they first described changes in the aorta as characteristic of syphilis. For many years the failure to find spirochetes in the aorta was used as an argument against the specificity of the lesions before these lesions were universally accepted as characteristic of syphilitic invasion of the aorta.

It impresses me as being rather unfortunate that the discussion of syphilis of the myocardium has centered around the question as to whether or not a specific form of myocarditis other than the gummatous type occurs. A care-

ful study of the excellent review by Saphir [36] obviously discloses that gummatous changes of the myocardium have been reported in many instances. This author in the beginning of his discussion stated that gummatous changes would not be reviewed. However, in 138 chronological case reports which he had reviewed, there were 66 instances in which reference to gummatous changes was made. Recently Sohval [46] stated that "the acquired tertiary syphilitic disease of the heart (exclusive of syphilitic aortitis with commissual involvement) is infrequent. If one omits from consideration the controversial diffuse fibrous type, the disease may be said to assume the form of diffuse interstitial gummatous myocarditis or that of localized gummatous myocarditis."

Syphilis may affect the coronary arteries either by involving the ostium of the main branch or by producing an endarteritis of the terminal branches. Pincoffs and Love [47] have recently emphasized the importance of occlusion of orifices of the coronaries in cardiovascular syphilis. In their small series of syphilitic aortitis 71.4 per cent dying a cardiac death showed this lesion. Love and Warner [48] in a study of syphilis of the heart, coronary ostia and coronary arteries concluded that the lesion of the coronaries most commonly noted was an obliterative endarteritis of the arterioles and that stenosis of the coronary ostia produces the most marked myocardial lesion. They also believe that the myocardial lesions in syphilitic aortitis can be attributed to defective coronary circulation. It is well to direct attention to the fact that, when the ostium of the coronary artery is entirely occluded by syphilis and infarction results, the infarction in no way differs from that associated with arteriosclerosis.

While syphilis of the myocardium is uncommon, there are clinical reports (Brooks,[49, 50] Coombs,[51] Carter and Baker,[52] Blackford and Boland,[53] Magill [54]) which suggest that it occurs more frequently than pathological studies indicate. If additional methods of study of the myocardium could be found and if more consideration were given to changes affecting the coronary arteries and to gummatous changes, it is possible that the pathologists and clinicians would be more in accord.

I have reviewed all the cases that I can find of syphilis of the myocardium since 1918, the time when Herrick [4] directed attention to the clinical picture of myocardial infarction, and have been unable to find any reported cases of syphilis of the myocardium with electrocardiographic and pathological studies and findings that resemble the picture of infarction of the myocardium, with the exception of two instances occurring in the Massachusetts General Hospital. The first patient,[55] a male of 58 years of age, who had had a long anginal history, suddenly died following severe precordial pain. Coronary sclerosis and cardiac infarction were diagnosed. Autopsy showed "the ostium of the right coronary artery completely blocked by a gummatous process. No thrombosis of the coronaries or large infarction of the myocardium was found; however, numerous small fibrous scars were present in the myocardium, particularly in the interventricular septum. The histology of these suggests a luetic process rather than the ordinary fibrosis following circulatory block."

The second instance,[56] a male of 26 years of age, had an interesting history of three admissions over an eight months' period; in the first admission for jaundice the diagnosis was catarrhal jaundice; in the second because of severe, non-localizing pain and jaundice, a diagnosis of cirrhosis of the liver was made and in the third because of severe precordial pain the condition was diagnosed

as syphilitic heart disease. Autopsy findings supported this last antemortem diagnosis by revealing syphilitic cardiac lesions including myocarditis.

Langeron [57] reported an interesting case in which the clinical picture of myocardial infarction was present. However, with the final episode no electrocardiographic studies were reported. Autopsy revealed closure of the ostium of the coronary artery. No evidence of infarction was found.

The age of my patient, the history of syphilis, and later skin manifestations justified the opinion that the myocardial damage was associated with syphilitic lesions involving the orifice of the coronary artery and this was the diagnosis on the second day of admission. However, the course and the duration of the illness made the diagnosis unlikely and consequently the final diagnosis was acute myocardial infarction due to coronary thrombosis.

The case is of interest because at autopsy no occlusion of the coronary arteries was found. However, microscopic studies disclosed definite myocardial damage associated with gummata. Careful search for spirochetes in the heart muscle gave negative results. These findings are significant and important because all the symptoms, signs, laboratory and electrocardiographic evidence considered characteristic of myocardial infarction were present. Of special interest in this case are the electrocardiographic findings relative to the R T and S T changes which were of the type usually considered characteristic of myocardial infarction. The autopsy findings support the clinical and experimental observations,[58, 59, 60, 61, 62] that the R T and S T changes in the electrocardiogram are associated with disturbance of the myocardium.

Summary

A case of acute gummatous myocarditis simulating myocardial infarction is presented. The history, physical examination, laboratory findings, electrocardiographic evidence and clinical course usually considered characteristic of acute myocardial infarction were present. The age of the patient, the history of syphilis, and the secondary skin manifestations justified the admission diagnosis of myocardial infarction from closure of the ostium of the coronary artery due to syphilis; however, because of the duration of the illness the final antemortem diagnosis was acute myocardial infarction due to coronary thrombosis. The autopsy revealed patent coronary arteries, and active granulomatous myocarditis with multiple caseating foci.[63] No spirochetes were discovered in the heart muscle. The patent coronary arteries and the extensive myocardial involvement support the theory of the myocardial origin of the R T and S T changes which were found in the electrocardiogram. It is suggested that gummatous myocarditis probably occurs more commonly than has been realized, and that it has not been recognized because too much attention has been given to the yet not generally accepted specific interstitial myocarditis of Warthin. Gummatous myocarditis is presented as another condition to be differentiated in the diagnosis of myocardial infarction.

Conclusion

1. While the diagnosis of coronary thrombosis is usually not difficult, occasionally errors are made.

2. Review of the literature reveals that there are conditions which closely simulate coronary thrombosis.

3. Whenever the clinical picture of myocardial infarction occurs in a young person who has a history or signs of syphilis, the possibility of syphilis affecting the ostium of the coronary arteries or the myocardium should be carefully considered.

4. Evidence is presented to support the theory that the R T and S T changes in the electrocardiogram indicate disturbance of the myocardium.

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A CASE OF PERNICIOUS ANEMIA AND CHRONIC LYMPHATIC LEUKEMIA *

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The combined occurrence of leukemia and pernicious anemia in one individual is undoubtedly rare. In 1900, Leube observed a patient with findings suggestive of both conditions, to which he gave the name "leukanämie." Since then a number of such cases have been reported, chiefly in the German literature. Sinek and Kohn [1] in 1930 reviewed the reported cases and came to the conclusion that most of them were either a true leukemia with a macrocytic type of anemia, or pernicious anemia with a leukemoid (myeloid) white cell picture. They described a case which they had followed for two and a half years, in which they had made a diagnosis of myeloid leukemia superimposed on a pre-existing pernicious anemia. However, their evidence for the diagnosis of pernicious anemia is not conclusive. While their patient presented a macrocytic anemia, glossitis, increase in serum bilirubin and achlorhydria, no reticulocyte response was recorded and there was only a slight gain in the red count following liver therapy. Beiglböck [2] reported a case of subleukemic myeloid leukemia

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with a clinical picture of pernicious anemia, and also reviewed the literature on the subject. The same objection may be raised to the diagnosis of pernicious anemia in his case as in that of Sinek and Kohn.

We wish to report a case recently studied at the Cincinnati General Hospital in which we feel the diagnosis of both chronic lymphatic leukemia and pernicious anemia is fully justified.

Case Report

The patient, a white male, aged 75, was admitted to the Medical Service of the Cincinnati General Hospital on March 15, 1934. He had been in fairly good health until one year before, when he developed an aching pain in his back, shoulders and thighs, which became progressively worse. He had also noticed increasing weakness and dyspnea on exertion, and more recently some edema of the ankles. His appetite had been fairly good and he had been partaking of an adequate diet, particularly as regards meat and green vegetables. He had not lost weight. There had been some tingling and numbness of the extremities. He had noticed some enlargement of the lymph nodes on the right side of his neck for the past 15 years, but had not been conscious of any recent increase in their size. His general health had been good. In 1927 he underwent an appendectomy for chronic appendicitis in another hospital. No blood counts were recorded at that time. The remainder of the history was not significant.

Physical examination revealed an elderly man, with white hair and a sub-icteric tint to the skin and sclerae. There were no manifestations of purpura. Definite pallor was present. The fundi showed moderate vascular sclerosis and old focal chorioretinitis in the right eye. There was some congestion and edema of the nasal mucosa. The teeth were worn and pyorrhea was present. The tonsils were small and atrophic. The tongue was pale, clean and somewhat smooth around the edges; the papillae were not definitely atrophied. The thyroid was not remarkable. A generalized lymphadenopathy was present, with involvement of the cervical, submaxillary, supraclavicular, infraclavicular, axillary, epitrochlear and inguinal nodes. The glands varied in size from that of a pea to a walnut. They were discrete, firm, not tender and freely movable. The lungs were not remarkable except for moderate senile emphysema. There was no cardiac enlargement as determined by percussion or roentgen-ray. A systolic murmur was heard along the left sternal edge. The rhythm was regular, and the sounds were distant. The peripheral vessels were moderately thickened. The blood pressure was 120 mm. of mercury systolic and 85 diastolic. The liver extended 8 cm. below the right costal margin; it was firm, smooth and presented a sharp edge. The spleen extended 6 cm. below the left costal margin and was firm and slightly tender. No other abdominal masses were felt. A midline ventral hernia was present. There was moderate soft pitting edema of the ankles. The deep reflexes were absent. Position sense was intact. Vibratory sense was absent over the lower extremities. Rectal examination was negative.

The results of various laboratory examinations on admission were as follows. There were 1,200,000 red cells and 40 per cent hemoglobin (Sahli). The white count was 85,800 and the differential smear showed 93 per cent lymphocytes of varying ages, 5 per cent monocytes and 2 per cent neutrophiles. The red cells showed poikilocytosis and macrocytosis. The mean corpuscular volume was 111, mean corpuscular hemoglobin 39.8 and mean corpuscular hemoglobin concentration 36.1. The platelets were apparently reduced in number. The urine was negative except for a trace of albumin, which later disappeared. A gastric analysis showed no free HCl following the injection of ½ mg. of histamine, and a total acidity of 6. The Kahn test on the blood was negative. The clotting and bleeding times were normal. The icteric index was 9.7 and the serum bilirubin gave an indirect Van den

Bergh reaction. There was no retention of bromsulphalein ½ hour after a dose of 2 mg. per kilogram of body weight. The serum protein was 5.71 grams. The non-protein nitrogen of the blood was 26 mg. per cent.

The clinical picture together with a white cell count of 85,800, of which over 90 per cent were lymphocytes, established the diagnosis of chronic lymphadenosis (chronic lymphatic leukemia). Because of the high color index and the presence of many macrocytes, it was felt that the patient was also suffering from pernicious anemia. This was further borne out by the histamine achlorhydria, the lack of vibratory sensation over the lower extremities and the hematocrit values.

Accordingly, treatment was begun with liver extract intramuscularly. He was given a total of seven injections, each derived from 100 grams of liver, over a period of 9 days. The reticulocytes, which had varied between 1.5 per cent and 2.5 per cent, began to rise 7 days later, and within two days reached a peak of 16.5 per cent (chart 1). They then fell rapidly to the pre-treatment level, which was reached in 18 days. Further treatment consisted in the administration of 30 grams of Ventriculin daily.

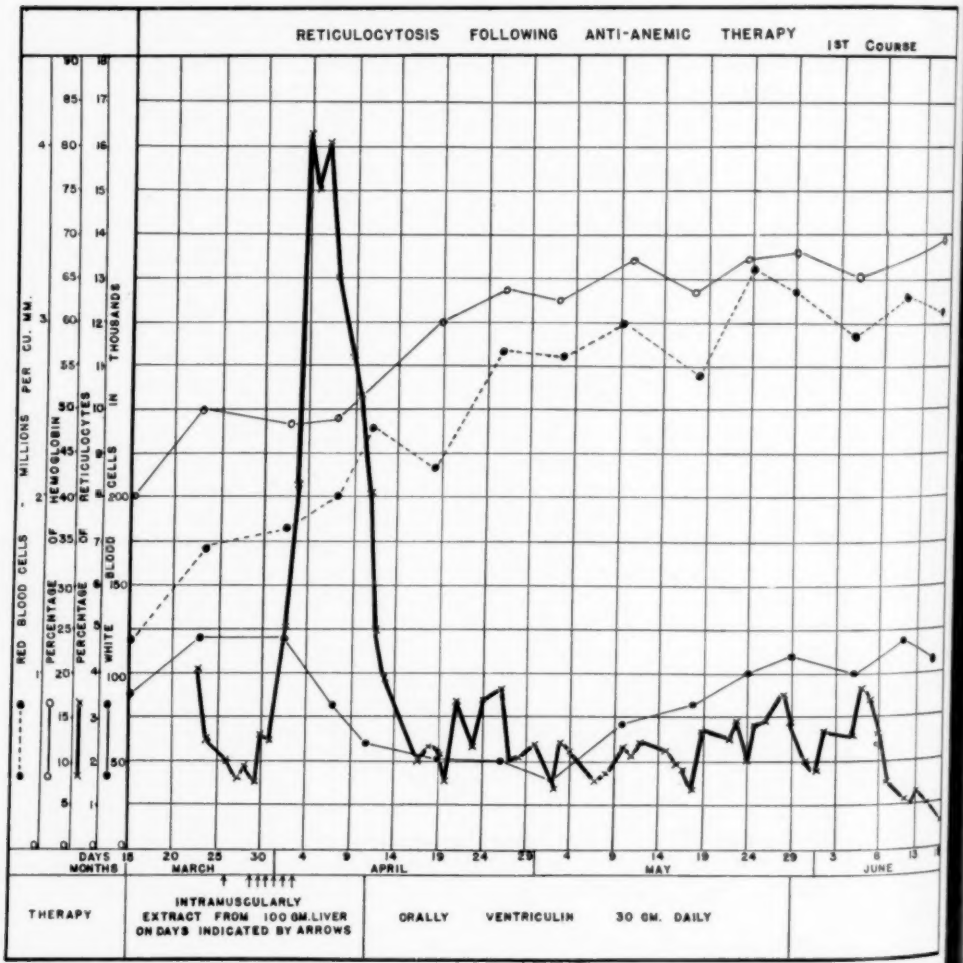

CHART 1.

The red count rose gradually from 1,700,000 on March 28, to reach a maximum of 3,300,000 on May 24. There was a corresponding increase in the hemoglobin from 50 per cent to 68 per cent during the same interval. During the remainder of this period of treatment, the reticulocytes varied between 1.5 per cent and 3.7 per cent. The white count during this period fell gradually from 120,000 to 40,000 and then rose to 110,000. The differential blood picture continued to show a predominance of old and young lymphocytes. After three weeks of treatment, however, there occurred a small increase in the percentage of neutrophiles, and later there was a transient rise in eosinophiles, which numbered 7.5 per cent on March 27.

In order to rule out coincidence, it was decided to see if a reticulocyte response could be obtained a second time. Accordingly, all anti-anemic therapy was discontinued for a period of eight weeks, during which time the bone marrow showed little erythropoietic activity. Almost daily reticulocyte counts varied between 0.5 per cent and 1.5 per cent. The red count dropped to 1,800,000 and the hemoglobin to 44 per cent. The white count rose to 230,000 with over 95 per cent lymphocytes. On August 22, treatment with anti-anemic substances was resumed. Extract derived from 300 grams of liver was given intramuscularly during a period of one week, in

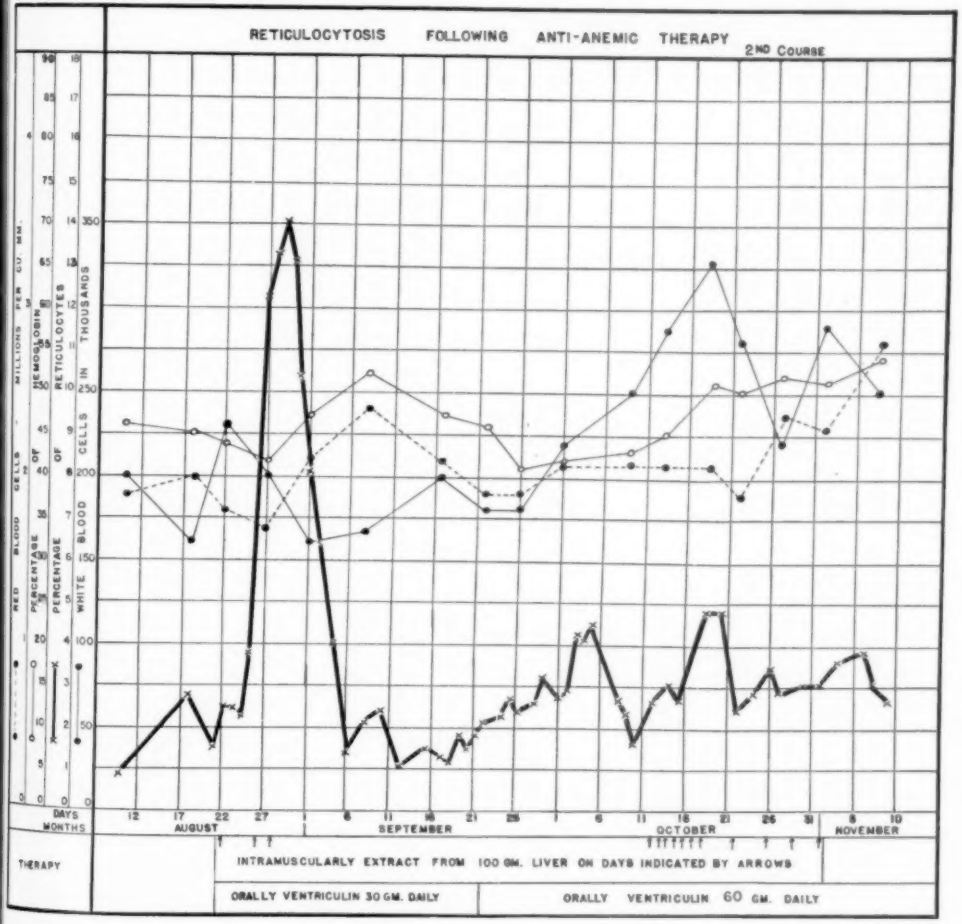

CHART 2.

TABLE I

Partial List of Blood Counts (Almost Weekly Intervals)

Date	R.B.C. (Mill.)	Hgb. (Sahli)	W.B.C. (Thous.)	Lymphs. %	Mon. %	Pmn. %	Eos. %	Bas. %	Lymphobl. %	Remarks
1934										
3–15	1.2	40	85.8	100.0	0.0	0.0	0.0	0.0	0.0	
3–28	1.7	50	120.0	99.0	0.0	1.0	0.0	0.0	0.0	7 injections 3 c.c. liver extract
4–2	1.8	48	120.0	95.0	0.0	5.0	0.0	0.0	0.0	
4–7	2.0	49	80.0	95.5	0.5	4.0	0.0	0.0	0.0	
4–11	2.4		60.0	88.5	0.0	11.0	0.5	0.0	0.0	Ventriculin, 30 gm. daily
4–19	2.2	60	50.4	90.5	1.0	7.5	1.0	0.0	0.0	"
4–26	2.8	63	50.0	76.0	1.5	12.0	7.5	0.0	3.0	"
5–2	2.8	62	40.0	89.5	1.5	7.0	2.0	0.0	0.0	"
5–10	3.0	67	70.0	93.5	0.0	3.5	0.0	0.0	3.0	"
5–18	2.7	63	80.0	94.5	0.0	4.0	0.5	0.0	1.0	"
5–24	3.3	67	100.0	87.5	1.5	10.0	0.5	0.0	0.5	"
5–29	3.2	68	110.0	91.0	0.0	4.5	2.5	0.0	2.0	"
6–5	2.9	65	110.0	86.5	1.0	7.0	5.5	0.0	0.0	No treatment
6–11	3.2	67	120.0	94.5	0.5	2.0	1.0	0.5	1.5	"
6–16	3.1	69	110.0	96.0	0.5	3.0	0.5	0.0	0.0	"
6–22	3.1	61	130.0							"
6–28	3.1	63	90.0	96.5	0.0	1.0	1.5	0.0	1.0	"
7–5	2.5	58	145.0							"
7–12	2.3	55	190.0							"
7–17	2.6	60	200.0	95.5	0.0	1.5	2.0	0.0	1.0	"
7–27	2.4	52	150.0							"
8–10	1.9	46	200.0	97.0	0.0	1.0	0.5	0.0	1.5	"
8–18	2.0	45	160.0							"
8–22	1.8	44	230.0							3 injections 3 c.c. liver extract
8–27	1.7	42	200.0	96.5	0.5	1.0	0.5	0.0	1.5	Ventriculin, 30 gm. daily
9–1	2.1	47	160.0	91.0	0.5	5.0	2.0	0.0	1.5	"
9–8	2.4	52	166.0							"
9–17	2.1	47	200.0	92.5	1.0	3.5	3.0	0.0	0.0	"
9–22	1.9	46	180.0							"
9–26	1.9	41	180.0	99.0	0.0	0.5	0.0	0.0	0.5	"
10–1	2.1	42	220.0	98.5	0.0	0.5	0.5	0.0	0.5	Ventriculin, 60 gm. daily until death
10–9	2.1	43	250.0	93.5	1.0	3.0	1.0	0.0	1.5	
10–13	2.1	45	290.0	94.5	0.0	2.5	2.0	0.0	1.0	11 injections, 3 c.c. liver extract
10–18	2.1	51	330.0	97.0	0.0	1.0	1.0	0.0	1.0	
10–22	1.9	50	280.0	96.0	0.5	1.0	1.0	0.0	1.5	
10–27	2.4	52	220.0	97.0	0.0	3.0	0.0	0.0	0.0	
11–1	2.3	51	290.0	95.0	0.5	2.5	0.0	0.5	1.5	
11–7	2.8	54	250.0	95.5	0.0	3.5	0.5	0.0	0.5	
11–12	2.6	53	240.0	98.5	0.0	1.0	0.5	0.0	0.0	
11–19	2.5	53	270.0	98.5	0.0	1.0	0.0	0.0	0.5	
11–26	2.4	49	230.0	94.5	0.5	2.5	0.5	0.0	2.0	3 c.c. liver extract
12–6	2.3	47	30.0	94.0	0.5	5.0	0.5	0.0	0.0	X-ray therapy
12–12	2.2	47	40.0	92.5	0.0	6.0	1.0	0.5	0.0	
12–28	2.6	52	90.0	97.0	0.5	1.5	0.0	0.0	1.0	
1935										
1–7	2.0	48	3.4	74.0	0.0	21.0	4.0	1.0	0.0	
1–24	1.9	41	5.0	79.0	2.0	18.0	1.0	0.0	0.0	
2–14	1.9	43	5.7	77.0	9.0	5.0	8.0	1.0	0.0	
3–4	2.1	46	44.3	88.0	0.5	10.0	1.0	0.0	0.5	

addition to 30 grams of Ventriculin daily. A rise in the reticulocytes again occurred, beginning on the third day and reaching a maximum of 14.1 per cent on the seventh day and returning to the pre-treatment level on the seventeenth day (chart 2). The red count and hemoglobin did not increase as much as before, reaching a level of 2,400,000 and 52 per cent respectively after three weeks. The increase was not maintained, and by the end of September the values had fallen to 1,900,000 and 41 per cent respectively. The dosage of Ventriculin was then increased to 60 grams a day, and in October he was given 11 injections of liver extract. This produced a slight prolonged reticulocytosis and later an increased red count and hemoglobin, the red cells reaching 2,800,000 and the hemoglobin 54 per cent on November 7. The white count did not fall during this second course of treatment, but ranged between 160,000 and 330,000.

An attempt was made to demonstrate the presence or absence of the intrinsic substance in the patient's gastric juice by incubating it with material containing the so-called "extrinsic" factor; but sufficient quantities of gastric juice could not be obtained.

The patient was given 60 grams of Ventriculin daily for the remainder of his illness. The red count gradually fell to 1,900,000 and the hemoglobin to 41 per cent. In December and again in January 1935, he received roentgen-ray therapy over the spleen and cervical nodes, which resulted in a marked drop in the number of white cells.

It is to be noted that the first reticulocyte response was slightly delayed, and submaximal, considering the large amount of potent material given, and that the red count and hemoglobin never reached normal levels. We believe that this may be explained by the fact that the bone marrow was so infiltrated with leukemic tissue as to obviate a normal response. Nevertheless, the red cell count and hemoglobin were increased to the level usually seen in leukemia in an advanced stage.

The patient remained in the hospital until his death one year later. During his stay almost daily studies were made of his blood. Some of these are recorded in table 1. His general condition remained about the same, except for signs of myocardial weakness, until late in February 1935, when he developed a purulent otitis media. Soon after this he contracted pneumonia, which proved fatal on March 6, 1935. Autopsy was performed four hours after death by Dr. James Mack.

The significant findings at necropsy were as follows. There was a generalized lymphadenopathy involving the cervical, infraclavicular, epitrochlear, axillary, inguinal, femoral, mediastinal and abdominal nodes. The glands were soft and yellow in color, and frequently as large as walnuts. There was some myocardial degeneration and fibrosis. The liver weighed 2580 grams, and presented numerous very small nodules on its surface. On section there was a large amount of yellow mottling. The spleen was likewise enlarged, weighing 625 grams. It was soft, with a tense capsule and a smooth uniformly pale red pulp. Microscopically, the lymph nodes were filled with a solid mass of small lymphocytes which completely destroyed the internal structures. There was also evidence of leukemic infiltration of the viscera. The spinal cord showed degenerative changes which were most marked in the posterior and lateral columns. Sections of the bone marrow showed lymphoid infiltration replacing to a great extent the myeloid elements. The erythropoietic centers presented a small number of megaloblasts, as well as normoblasts. Macrocytes were present in every field. The prostate, although grossly not remarkable, gave microscopic evidence of a chronic interstitial prostatitis and an early adenocarcinoma. Lobar pneumonia was present in the left lower lobe and confluent lobular pneumonia in the left upper and right lower lobes.

We believe that the diagnosis of chronic lymphatic leukemia in the case reported cannot be questioned. The enlarged spleen, enlarged lymph glands, per-

sistently high white count with predominance of lymphocytes and the anatomic changes are all typical of this disease. The diagnosis of pernicious anemia is also warranted in view of (1) the macrocytic anemia which responded on two occasions with a rise in reticulocytes and an increase in the red count and hemoglobin after the use of "specific" anti-anemic therapy, (2) achylia gastrica, (3) loss of vibratory sense and (4) degeneration of the posterior and lateral columns of the spinal cord.

No attempt is made to correlate the etiology of these two conditions by the study of this case. In all likelihood, the existence of the two diseases in the same individual was a coincidence.

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LIPEMIA ACCOMPANIED BY ATHEROMATOUS AND OCCLUSIVE VASCULAR DISEASE: REPORT OF A CASE AND PARTIAL REVIEW OF THE LITERATURE*

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According to Rowland and to Pick, the disorders of lipid metabolism may be classified as essential or primary, and symptomatic or secondary. Among the primary disturbances Rowland considered essential xanthomatosis, with involvement of skin, mucous membranes, tendon sheaths, or viscera; Niemann-Pick disease; Schüller-Christian disease, and Gaucher's disease. As Rowland said, there are cases that defy classification.

The group under present consideration is that which Pick described as the residual group, Rowland as essential xanthomatosis. There is in this group no characteristic age, sex, or racial distribution. The clinical manifestations are extremely varied. There are a number of cutaneous types, varying from the small xanthelasma palpebrarum to general eruptive forms. The mucous membranes may be involved, as in the cases of Finney, Montgomery, and New. They reported from The Mayo Clinic two cases of xanthoma multiplex involving the larynx and trachea, associated with diabetes insipidus. Small subcutaneous xanthomas may occur, and rarely, larger xanthomas may occur as tumors on tendon sheaths and aponeuroses. Visceral involvement of varying extent and location may also occur. In some cases vascular involvement may be the chief manifestation.

These various manifestations may be observed separately or in various com-

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binations. The characteristic histologic feature of this group of cases is the presence in the involved regions of large, clear, foamy cells containing lipids, in which cholesterol and its esters usually predominate. The lipids in the blood may be normal or elevated, and if elevated there is practically always hypercholesterolemia. Robertson and Warren reported a case in which the diagnosis depended on biopsy of a lymph node; the deposits of lipid occurred principally if not entirely in the lymph nodes, and the lipids in the blood were not increased.

Investigations have revealed a large number and wide variety of conditions in which a disturbance of the lipids is found as a symptomatic or secondary manifestation. Even excitement may produce temporary hypercholesterolemia; Lyons found this to be abolished in cats by sympathectomy.

Prolonged obstruction of the biliary tract produces an increase in the level of cholesterol in the blood. Gardner and Gainsborough reported this to be true in a case of obstructive jaundice, in a case of stone in the common duct, and in a case of carcinoma of the pancreas and gall-bladder with biliary obstruction. Hypercholesterolemia was observed in a case of obstructive jaundice reported by Brain and Byrom, and in cases of subacute yellow atrophy and subchronic atrophy of the liver reported by Adler and Lemmel. Similar changes occur in most stages of catarrhal jaundice.

An increase of cholesterol and cholesterol esters in the blood often is found in renal disease, notably nephrosis; in two such cases Lichtenstein and Epstein found exceedingly high levels for cholesterol. In cases of acute nephritis, Maxwell found the increase in cholesterol to be proportional to the amount of edema; he observed high values for cholesterol in cases of chronic nephritis with or without edema. Ashe and Bruger found high values for cholesterol in cases of chronic glomerulonephritis, in some of which the value for urea in the blood was normal, in others elevated. Hurxthal, and also Myers, found an increase in the cholesterol in the blood of patients with extensive arteriosclerosis. Westphal found that 71.2 per cent of eight patients with hypertension had high values for blood cholesterol, and this was true even in early life.

High values for blood cholesterol may also be observed in cases of diabetes mellitus. Oppenheimer and Fishberg observed that: "The old blood-letters were well aware that under certain conditions, notably severe diabetes mellitus, the blood may contain an excess of fat so great that, on being left to stand, a thick creamy layer separates to the top." Jaffe, Morris, and Schonfeld have reported a case of lipemia retinalis in a diabetic with marked hyperlipemia. Lepard reported a case of diabetes with well-marked hyperglycemia and hyperlipemia, cutaneous xanthomas, and lipemia retinalis. Curtis, Sheldon, and Eckstein observed that, to have a severe lipemia, the diabetes must be severe, and that the lipemia disappears under control. Collins has said that high values for blood fats, and Rabinowitch that high values for blood cholesterol, indicate an unfavorable prognosis in cases of diabetes.

Hurxthal stated that, in myxedema, the percentage of increase of cholesterol in the blood is so much greater than the percentage of decrease in the rate of metabolism that the value for cholesterol stands out as an indicator of thyroid deficiency. Mason, Hunt, and Hurxthal reported the observation of a series of cases with high values for cholesterol in the blood.

Kumpf found that prolonged bleeding leads to persistent lipemia in rabbits. Muller found that, regardless of the severity of the anemia, the initiation of a

remission in cases of pernicious anemia is characterized by a sudden increase in blood cholesterol, which during relapse was below normal.

Sternberg found increased values for cholesterol in the blood of patients with manic depressive insanity, and Hurxthal concluded that hypercholesterolemia is more frequent among patients with mental disease than among those with general disease. McQuarrie, Husted, and Bloor concluded regarding epileptics that: "a relative increase of plasma lecithin favors the occurrence of seizures, while a relative increase in cholesterol tends to prevent them." In a study of 100 epileptic and 32 nonepileptic children, McQuarrie, Bloor, Husted, and Patterson found no significant difference in the range of values for plasma cholesterol or in its variability in the two groups. Rosen, Krasnow, and Notkin found that the average values for the cholesterol and lecithin content of the blood in epilepsy were normal.

Rosen and Krasnow observed that, in general, the cholesterol content of whole blood tends to be high in dermatoses. In pregnancy, according to McEachern and Gilmour, cholesterol is increased, particularly in the last trimester. Diets rich in fat, such as the ketogenic diet, lead to an increase in the level of lipids in the blood. Bruger and Poindexter found normal lipid levels in obese individuals without complicating diseases. Prolonged starvation is said by McEachern and Gilmour to lead to an increase of cholesterol in the blood.

An abundant literature confirms the fact that the feeding of diets rich in cholesterol is followed in animals by the formation of arteriosclerotic lesions in various vessels. Ignastovski, in 1908, observed atheromas in the aortas of rabbits after feeding them milk and egg yolks, and this observation was confirmed in 1909 by Starokadomosky and Ssobolew, who found similar changes in the innominate, carotid, and subclavian arteries. Anitschkow and Chalatow concluded that cholesterol was the substance responsible for these changes, and in 1913 they produced, by the feeding of pure cholesterol to experimental animals, an aortic sclerosis similar to that observed in man.

Anitschkow, in 1924, found that local vascular changes may be produced in the absence of large increases of lipids if the vessel be traumatized. Whether, as Harris and Lipkin have said, these observations are applicable to man is another question. Leary has observed that man is the only animal that ingests eggs and milk during a lifetime, and man is the only animal that dies in early life from coronary sclerosis and acquires atherosclerosis almost universally in advanced years.

There are a number of reported instances of atheromatous or xanthomatous infiltration of the cardiovascular system in a variety of conditions associated with elevated levels of lipids in the blood. Fagge, in 1873, reported the occurrence of xanthomatous infiltration of the left auricle, aorta, and pulmonary, innominate, and carotid arteries of a patient who had long suffered from obstructive jaundice and had numerous cutaneous xanthomas. In the same year Maxon reported the observation of atherosclerosis in a patient with hepatic cirrhosis and cutaneous "xanthelasma." A girl of 11 years, who had cutaneous xanthomas, was examined by Lehzen and Knauss who in 1889 reported that they found yellow, raised patches on the mitral valve, producing incompetence; similar changes were observed in the aorta and pulmonary, coronary, and left carotid arteries. Pollosean, in 1890, and Low, in 1910, observed precordial murmurs

in patients who had xanthomas on the skin, but necropsy was not performed in either instance.

In 1925 Oppenheimer and Fishberg observed atherosclerotic areas containing large "foamy" cells in the cardiovascular system of a patient who had had papular xanthomatosis and who had died in diabetic coma; similar changes were found in two cases reported by Lutz in 1914. Knox in 1919 observed in a case of Gaucher's disease rows of swollen granular cells, similar to those in the spleen, surrounding the muscularis of some of the small arterial twigs. Siegmund in 1921 noted in a case of Gaucher's disease that the endothelium of vessels in the skin, heart, and kidneys contained large lipid cells. Benda in 1924 described the occurrence of xanthomatosis of the pulmonary veins in a case of nephrosis with marked lipidemia. Velhagen in 1914 reported a case of hemorrhagic glaucoma in which there were large clear cells between the endothelium and internal elastic membrane of the central artery of the retina.

Case Report (Abridged)

The patient in the present case, a married woman, aged 55 years, came to the Clinic May 7, 1934, complaining principally of weakness, exhaustion, spots before her eyes, and of headache. Her father had died of apoplexy, but the family history was otherwise negative. One of her children was living and well; one had petit and grand mal. The patient had been rather high-strung, had worried greatly, and had had morning headaches for at least 10 years. She had had insomnia and hot flashes for four or five years, but, until 1932, had considered herself in good health.

In August 1932, the patient had not felt well. Some cardiac weakness and a systolic blood pressure of 200 mm. of mercury were found. She had kept moderately quiet. In November 1932, she had suffered much fatigue and pounding in the head and had stayed in bed much of the time during the next four months. The metabolic rate had been normal. In bed, the blood pressure had fallen to 148 mm. of mercury. In June 1933, vertigo suddenly had developed, necessitating rest in bed; this had lasted until fall. In December 1933, the patient suddenly had become blind in the left eye for 15 minutes, and later had had scotomas of various kinds before both eyes. In February 1934, a similar attack had occurred, and she had seen vari-colored lights for two days; at times there had been hemi-vision. Later she had had a feeling as if someone were sitting on her chest; this had been accompanied by discomfort in, and slight disuse of, the left hand. There had been moderate dyspnea on exertion. The history otherwise was not significant.

At the time of examination the patient was found to have a mild elevation of systolic and diastolic blood pressure. On deep inspiration the liver edge was felt hard and sharp one inch (2.5 cm.) below the umbilicus in the mammary line. There was sclerosis, grade 1 +, of the retinal arteries, of the hypertensive type; exaggerated disk rings; and mild choroidal degeneration in the region of the maculae. There was no evidence of lipemia in the retinal vessels. Three specimens of urine showed no significant abnormality. Serologic test of the blood for syphilis was negative. Roentgenograms of the head and of both humeri were negative, and those of the lumbar portion of the spine, pelvis, and upper ends of the femurs revealed hypertrophic changes in the lower thoracic and upper lumbar portions of the spinal column but otherwise no structural changes in bone. A roentgenogram of the thorax revealed only slight cardiac enlargement. The value for cholesterol was 667 mg. per 100 c.c. of plasma, total fatty acids being 1971 mg., and total lipids 2638 mg. The basal metabolic rate was + 8 per cent. Electrocardiograms were normal save for diphasic T-waves in derivations I and II and iso-electric T-waves in derivation III.

Tests of liver function by the Rowntree-Rosenthal method showed the presence of dye in the serum at the end of one hour; it was impossible to determine the degree of retention of dye owing to the high grade lipemia. Total values for lipids in the urine were 2.2 mg. per 100 c.c., in a total of 1115 c.c. of urine constituting a 24 hour specimen. Neurologic examination strongly suggested some cerebral or retinal vascular spasm with residual scotomas, but the neurologic findings were extremely few.

A diagnosis was made of moderate hypertension, arteriosclerosis of the central nervous system and coronary arteries, general arteriosclerosis, moderate enlargement of the liver, cardiac hypertrophy, and lipemia of unknown origin. Because of the unexplained lipemia, together with the absence of significant changes in bony structures, the suggestion of essential xanthomatosis was made and a diet low in fat was recommended.

The patient was permitted to return to her home, where, at our suggestion, a test of sugar tolerance was made; a diabetic type of glucose tolerance curve was obtained. She was given a rather high carbohydrate diet with limitation of fats. Insulin was administered for a time but its use was discontinued because of untoward effects.

The patient returned to the clinic August 2, 1934; she had lost 19 pounds (8.6 kg.) and had gradually become weaker. There was weakness but not paralysis of her entire left side, which at times had felt numb; it had tingled and prickled. Sometimes it had been difficult to articulate. The patient gave evidence of loss of weight, but she did not appear acutely ill. There was mild hypertension and the peripheral vessels were sclerotic, grade 2. The heart was slightly enlarged; the liver was palpable on deep inspiration, three fingers' breadth below the costal margin. Gross examination of the eyes gave essentially negative results. The neurologist thought that, on the basis of the complaints referable to the central nervous system, the symptoms were probably on an arteriosclerotic basis.

One week after admission the patient complained of feeling dizzy and of weakness of the left side of her body. Shortly thereafter complete motor paralysis of the left side developed, including the external ocular muscles, together with great difficulty in swallowing and speaking. Spinal puncture revealed nothing abnormal. The most likely diagnosis seemed to be cerebral and pontine thrombosis, although brain tumor or hemorrhage could not be excluded. Because the lesion might be a xanthoma, four roentgen treatments of the brain were given on four successive days. For a short time the patient was given 50 gm. of fat per day, but later fat consumed varied from 6 to 50 gm. each day. The total daily caloric intake varied from 875 to 1890 during the period of hospitalization. There was gradual improvement of the patient's eyes, speech, and limbs.

Roentgenograms of the head, spinal column, and pelvis revealed no significant changes. Tests of liver function did not reveal retention of dye. There were 30 mg. of urea and 81 mg. of glucose per 100 c.c. of blood. Glucose tolerance was normal. All values for plasma lipids are indicated in table 1. Twenty-five days after this admission the glucose tolerance again was found normal.

The patient returned October 2, 1934. After leaving the hospital in August she had improved rapidly for two weeks; after two weeks the improvement had been more gradual. About 10 days before this admission she had had "trembling" in the abdomen, which had been generalized and intermittent, and about the same time she had noticed increased nervous tension, which had persisted. There had been occasional aching in the left arm, and once, a severe pain in it. In the last week she had had a sensation of pressure over the left part of her chest, which had not been accompanied by pain or cardiac palpitation. Her left hand was hypersensitive to heat; the fingers were still somewhat stiff and "felt full." There had been edema of the left hand since the onset of hemiplegia. She had gained 15 pounds (6.8 kg.) in the month prior to this admission.

On examination, there was moderate pallor of the skin and mucous membranes; the pupils reacted to light. The heart was slightly enlarged to the left; the tones were good and murmurs were absent. There was peripheral sclerosis, grade 2, and a mild hypertension. The liver edge was palpable three fingers' breadth below the costal margin in the midclavicular line. The spleen was not palpable. There were no abdominal masses and no enlargement of the lymph nodes. There was abortive nystagmus on looking to the left, and slight left facial weakness. Deep reflexes were hyperactive on the left side. There was a positive Hoffman sign in the left hand, but a negative Babinski reflex. Abdominal reflexes were not elicited except in the left lower quadrant, which was hyperactive, grade 2.

The eyes were essentially the same as on the previous visit except for improvement in the strength of the muscles. Four specimens of urine were essentially negative. The values for hemoglobin and the erythrocyte and leukocyte counts were normal; values for lipids in the blood are given in table 1; those for blood urea and sugar were within normal limits. The electrocardiogram was normal save for diphasic T-waves in derivation I. The increase in blood fats despite the low fat diet could not be entirely explained, but it was thought best to continue the diet with the low fat content. For five nights in succession the patient had attacks of severe precordial pain, radiating to the left arm. She of course had not exercised and thought that the pain was not related to excitement. She did state that the pain came on after eating. Physical examination of the heart revealed no abnormality, but, because of the history and the diphasic character of the T-wave in derivation I in the electrocardiogram, it was thought that the attacks were probably anginal in origin. About this time it was thought advisable to lower the caloric content of the diet to 550 each day; the intake of vitamins and minerals was supplemented by giving brewer's yeast (Harris), proprietary tablets of vitamins A and D (Adex), and calcium phosphate.

Although an initial rise in cholesterol occurred on the fourth day, there was a rapid diminution in the fatty acids and total lipids (table 1). There was, however, little subjective improvement in the patient's condition and she continued to have

TABLE I

Lipid Values during Observation, Milligrams per 100 c.c.

	1934									
	5–11	8–4*	8–17	8–29	8–31	10–2	10–9	10–15	10–20	10–22
Cholesterol	667	354	278	333	416	454	567	430	302	387
Fatty acids	1971	530	666	986	1076	2732	1206	885		694
Total lipids	2638	884	944	1319	1482	3186	1773	1315	302	1081
	Grams per day									
Diet while in hospital	8–2		8–12				10–5			10–22
Carbohydrate	300		275				57			261
Protein	60		55				49			100
Fat	50		25				10			21

* On this date, lecithin 371 mg. per 100 c.c., and cholesterol esters 231 mg. per 100 c.c. of blood.

some pain in her left shoulder and arm. October 16, there was an increased weakness of the left arm and leg, with a subjective sensation of numbness. There was definite impairment of speech and deglutition. A rather marked, vertical nystagmus developed; horizontal nystagmus was still present on rotation to either side, and the strength of the right external rectus muscle was still impaired. There was no change in the ocular fields or fundi. October 19 the patient's condition was sufficiently improved to permit further roentgen therapy, and each of four segmental regions of the head was irradiated, one each day. Since the patient still had difficulty with mastication and deglutition and was weaker, it was deemed advisable, on October 22, to increase the caloric intake to 1633; the fat was still markedly limited, to 21 gm. daily. The carbohydrate allowance was 261 gm., the protein, 100 gm. Amino-acetic acid was given, one level teaspoonful four times daily.

In the next two days there was an appreciable improvement in the patient's condition; she felt much stronger and was able to sit up in bed for the first time in a week. On October 24 she felt particularly well, until about 6 p.m., when suddenly she had a severe and persistent pain in her left shoulder. This was controlled with some difficulty by opiates. After two hours the patient became unconscious; there was a gradual decline and she died.

Postmortem examination revealed extensive atheromatous changes in the arteries but no organic changes suggestive of any of the named lipid dyscrasias. The heart weighed 342 gm., and there was an increase in fat, grade 1 +. At the base of the left ventricle, anteriorly and laterally and extending to the posterior surface, a region supplied by the circumflex branch of the left coronary artery, there was an area of softening, grade 3, of the myocardium. The circumflex branch of the left coronary artery was completely occluded by a thrombus (figure 1). Atherosclerosis, grade 3 to 4, of the coronary arteries was found, and there was atherosclerosis, grade 2, of the thoracic aorta.

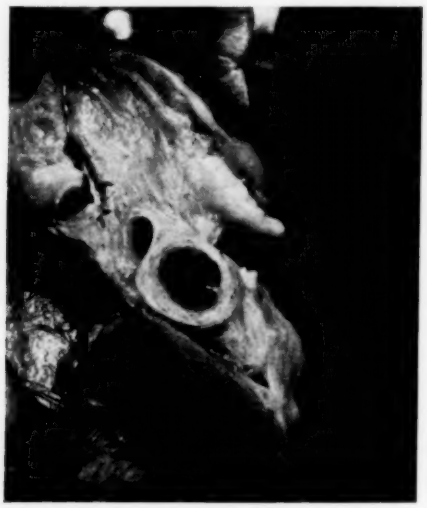

FIG. 1. Thrombus near origin of circumflex branch of left coronary artery; the atheromatous infiltration is easily seen.

The liver extended 1 cm. below the costal margin in the midclavicular line and weighed 1983 gm.; the cut surface revealed an increase of fat, grade 2, and fat could be seen on the cutting knife. The gall-bladder contained four stones. The spleen weighed 200 gm. and was slightly softened; the pancreas weighed 80 gm. and revealed

fat replacement, grade 1. The splenic artery was very tortuous and gave evidence of atherosclerotic changes, grade 3+; on cross section it appeared to be almost completely occluded. There was atherosclerosis of the abdominal aorta, grade 3 to 4, with extensive atheromatous abscesses (figure 2).

FIG. 2. Aorta, showing extensive atheromatous degeneration and formation of "abscesses."

The vessels of the brain showed extensive atherosclerotic changes, the basilar artery being completely occluded by sclerosis and thrombosis. There was slight generalized atrophy of the brain, an infarct measuring 2 by 1 cm. on the superior surface of the right lobe of the cerebellum, an infarct measuring 3 by 2 cm. in the

posterior apex of the occipital pole of each cerebral hemisphere, an infarct 7 mm. in diameter in the right superior olive, and a few small infarcts measuring up to 5 mm. in diameter in the right side of the pons.

Microscopic examination of the infarcted region of the heart revealed many islands of old and recent infarction, with dense connective tissue replacement in the old and pale-staining tissue and many leukocytes in the newly infarcted area. No intercellular or intracellular fat was seen in the heart except in the infarcted area. In the coronary arteries there was an eccentric intimal thickening, consisting of lipid material and cholesterol crystals. These changes varied in extent from small plaques to complete occlusion of the arteries; there was thrombosis in the region of the atheromatous abscess. In the left descending coronary artery there was complete occlusion and canalization (figure 3).

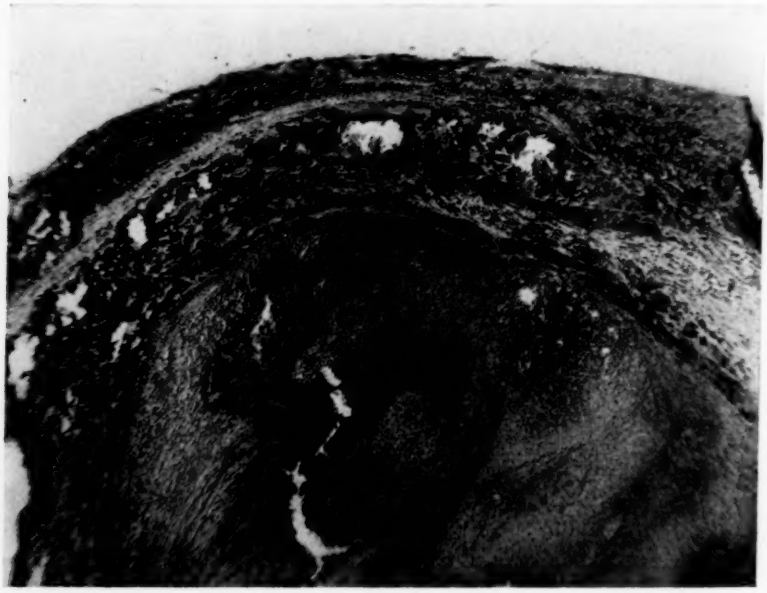

FIG. 3. Left descending coronary artery, showing thrombosis; the lipid infiltration of the entire wall of this vessel is visualized—black staining areas—(low power).

The section of the spleen contained small infarcts. There were scanty lipid deposits in an occasional reticulo-endothelial cell, but no foam cells could be found. In the liver there was moderate congestion and some central atrophy. A fine, fat dust was scattered diffusely within the cells; here, too, no deposits of lipid could be demonstrated that were characteristic of any described lipid dyscrasia. The suprarenal glands showed a rather extensive deposit of lipid, the intracellular lipid being present as droplets. There were lipid-containing cells arranged in radial fasciculi, extending from the capsule through the reticular layer. The alternate bands revealed a fine intracellular fat dusting. The changes were not, however, as pronounced as those sometimes seen in presumably normal glands. The kidneys were essentially normal, although occasional fine lipid droplets could be seen in the collecting tubules and in the intima of the arterioles. The splenic artery revealed extensive atheromatous changes, with complete occlusion in some places. The lymph nodes revealed no abnormality and there were no significant changes in the bone marrow.

Comment

There was nothing about the condition of this patient to suggest Gaucher's disease. Schüller-Christian, Niemann-Pick, and Tay-Sach disease were readily excluded on the basis of the patient's age. We felt that the case probably would be best classified as one of essential xanthomatosis and we treated the patient accordingly. No condition other than moderate hypertension and arteriosclerosis was present in which disturbed lipid metabolism has been reported to occur as a secondary manifestation. We do not believe that the degree of hypertension observed in this case, particularly in the absence of significant renal changes, can be considered to be the factor responsible for the disturbed metabolism of lipid. Although one glucose tolerance test was characteristic of diabetes, we feel that the observation of normal levels of blood sugar, the absence of glycosuria, and a normal glucose tolerance response on two occasions exclude the diagnosis of true diabetes mellitus. It would, therefore, seem that this is best classified as a case of so-called "essential" xanthomatosis, with localization primarily in the vascular system. Despite the extremely advanced vascular changes, there were no significant lipid deposits in any other part of the body.

It is interesting in this connection to note the experimental evidence of production of atherosclerotic changes as a result of diets high in cholesterol. So far as we were able to determine, our patient had always adhered to a well-rounded dietary; the elevation in lipid would seem to have been on the basis of an anomaly of lipid metabolism. It seems most reasonable to postulate this as the primary and the atherosclerosis as the secondary manifestation; however, the possibility must be considered that the atheromatous changes in the arteries were primary and the lipemia due to rupture of atheromatous "abscesses."

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EDITORIAL

HEAT CRAMPS

In recent years a considerable literature has sprung up in connection with the clinical condition which in the past has been called by various authors firemen's cramps, stokers' cramps, miners' cramps, cane cutters' cramps or mill cramps, and which is now usually designated by the more general name of heat cramps. This literature has been analyzed by Talbott * in a general review in which he includes also a presentation of his own studies in this field.

Heat cramps are a severe form of muscular cramps, occurring chiefly in the extremities, during or following heavy labor, at a high working temperature and in the hot season of the year. They are infrequently seen by the average physician but are well known to the industrial surgeons in the steel mills and in certain mines, as well as to ships' surgeons in the tropics.

These cramps are described as involuntary spasmodic contractions coming on either in isolated groups of muscles in the extremities, as for example in the flexors of the fingers, or affecting more widely the large muscles of the legs, of the arms, of the back or the abdominal wall. Even the facial musculature may be involved. The smooth muscles probably do not participate in the process.

In severe cases the cramps recur every few minutes, the interval lengthening as the attack wears off. The duration of the individual cramp is from one to three minutes and during this time the contracted muscles are stony hard or board-like. The pain is very severe in the stage of paroxysmal contraction but disappears in the interval. The duration of an attack of heat cramps may be from a few hours to several days.

As opposed to heat stroke and heat prostration, heat cramps present rather mild constitutional symptoms. There may be slight headache or vertigo. The temperature is within a normal range. The blood pressure shows no significant change. The pulse and respiratory rate are moderately increased. The severity of the pain in the severe cases may, however, seriously exhaust the patient. Death from uncomplicated heat cramps may occur.

Talbott has made an interesting study of the etiologic factors involved in the production of heat cramps. Foremost among these is the concurrence of a high working temperature and a high atmospheric temperature. In other words, it is in the season or in the geographic location where the worker is exposed to continuous high temperature that heat cramps are most frequent. In the steel mills of the Youngstown district more than 90 per cent of the hospitalized cases are admitted between April and October of each year. The temperature at which heat cramps occur is generally over

* Talbott, J. R.: Heat cramps, Medicine, 1935, xiv, 323–376.

100° F. Working temperatures in various industries are often extraordinarily high: 112° to 135° F. in sugar refineries (Coplin); 125° F. in the stoke-hole of a warship (Phelps); 150° F. in a pullman diner kitchen (Clendening). Even higher temperatures are encountered by certain workers in the steel industry.

Contrary to the general impression, the relative humidity of the working atmosphere was not found to be an important factor in the production of heat cramps.

Talbott does not discuss in detail the relationship of the character of the muscular work to the incidence of heat cramps. It is apparent from its industrial distribution that it is far more common among those doing heavy physical labor. There is some evidence also that the cramps are most apt to affect the muscles which have been most actively employed. The observation of cramps in pullman cooks indicates, however, that heavy muscular exertion is not an absolute essential. It is certainly, nevertheless, a more vital factor in the production of heat cramps than it is in the development of either heat stroke or heat prostration.

Defective general hygiene, ill health, inadequate assimilation of food, acute alcoholism and a recent attack of cramps were all found, from an analysis of the series of cases observed by Talbott in the Youngstown area, to be predisposing factors.

An important observation which has been made by a number of students of this condition is that the incidence of heat cramps is greatest during the first few days of a hot wave and that there is a decreasing susceptibility as the hot weather continues. This plainly suggests the presence of a process of adaptation of the body to continued environmental heat. From certain data available it seems probable that the mechanism of this adaptation may involve the amount and the composition of the sweat secreted. The observations of Moss * suggest that acclimatization to heat may involve a doubling of the sweat output, while those of Dill † indicate that adaptation includes the secretion of sweat containing a much reduced percentage of chlorides. The results of these studies are at present more suggestive than conclusive.

It is a point of definite value that the incidence of heat prostration is said to be greatest after the heat wave has continued for some time, since this difference from the time of highest incidence of heat cramps is strongly in favor of a fundamental difference in the pathogenesis of the two conditions. Further statistical data to soundly found this distinction would be desirable.

Talbott has made careful metabolic studies of 32 cases of heat cramps from the mills of the Youngstown area. Very marked changes in concentration of many of the constituents of the blood and urine were found,

* Moss, K. N.: Some effects of high air temperatures and muscular exertion upon colliers, Proc. Roy. Soc. London, Series B., 1923–24, xcv, 181.

† Dill, D. B., Jones, B. F., Edwards, H. T., and Oberg, S. A.: Salt economy in extreme dry heat, Jr. Biol. Chem., 1933, c, 755.

and as a result of these observations our knowledge of the condition has been notably advanced.

The findings in the arterial blood indicated a marked anhydremia. Serum protein was greatly increased on admission—in one instance to 10.6 grams per cent. The increase was found due to the globulin fraction. The serum protein fell toward normal levels during the first days in the hospital but this decrease was not strictly parallel to the improvement in the clinical condition. The concentration of the hemoglobin, as measured by the oxygen capacity, was increased in correspondence to the serum protein increase. The rise in number of red cells paralleled closely the increase in hemoglobin. The anhydremia did not consist only of serum water loss since there was also a loss of 1 to 5 per cent from the red cells. . The extent of the concentration of serum protein and hemoglobin was comparable to that found in severe cholera. Blood volume determinations were not made, and data on the specific gravity of the blood are not given.

It is interesting that in spite of these evidences of severe dehydration the amount of urine voided on the day of admission to the hospital was surprisingly large, varying between 400 and 800 c.c.

The concentration of electrolytes in the serum of patients with cramps was found altered even in the mild cases. The serum chloride and the serum sodium were consistently diminished. The concentration of serum chlorides on admission was only twice found above 100 m. eq. and in one case it was 79.8 m. eq. The minimum serum sodium concentration was 121.0 m. eq. and the maximum was 140.0 m. eq. The urine in most instances showed a relative absence of sodium and chloride and in severe cases this persisted for several days. During the first few days in hospital balance studies showed a marked retention of sodium, chloride and water with a resultant gain in weight which averaged 4.4 pounds. These findings confirmed and greatly extended earlier observations by Edsall, Raschewskaja and others.

Serum sodium was the only inorganic base whose concentration was decreased in patients suffering from cramps. The concentration of potassium in the serum was normal or increased 1 to 3 m. eq.; and there was likewise in many patients a distinct increase in calcium concentration. A maximum of 14.3 mg. per 100 c.c. of calcium was observed in two patients. On theoretical grounds the increase of calcium was considered greater than could be accounted for by the calcium binding power of the increased protein.

The variations in the arterial pH's covered a wide range but in most patients the reading was below 7.40, the apparent acidosis being explainable through loss of base. The pH of the urine on admission was usually about 5.0, a degree of acidity greater than was accounted for by the titratable acid found.

There was also noted an unexplained increase in the serum of inorganic

phosphates. The non-protein nitrogen was elevated 10 to 25 mg. per 100 c.c. above normal levels. Blood sugars were within the normal range.

An observation of great interest and possibly of importance was that in 14 of the 32 patients on admission the degree of oxygen saturation of the arterial blood was below 94 per cent and in one patient it was found to be 84.6 per cent.

Talbott's analysis of these data has led him to feel that the decrease of serum sodium and serum chloride bears the most constant and significant relationship to the occurrence and severity of the cramps. He feels that in each working subject a critical level exists for sodium and chloride, below which muscular cramps occur. The loss of serum sodium and chloride is presumably through excessive sweating.

The hypothesis is greatly strengthened by the striking therapeutic effects of the administration of sodium chloride as normal salt solution intravenously. In severe cases 600 to 1,000 c.c. of the saline solution were administered, and in all instances the cramps were relieved before the infusion was terminated and could not be brought back thereafter by artificial means. In less severe cases the ingestion hourly of a 1 grain salt tablet was effective. In the prevention of cramps the value of an increased salt intake has been claimed by a number of observers. It has been dispensed to workers in the form of salt tablets but recent opinion favors its introduction into the drinking water to produce a 0.1 per cent concentration. Such a solution is without perceptible saline taste.

The argument in favor of a specific relationship of lowered serum sodium and chloride to heat cramps would be further strengthened if data from the control series of heat prostration cases had been furnished showing the absence of any similar changes in the serum of these patients.

These studies mark a definite advance in our knowledge of this interesting condition. It is apparent that the entire mechanism of heat cramps is not yet clear and that many of the actual findings are unexplained; but definite data concerning one fundamental feature of this mechanism have been obtained. In how far this knowledge will yield insight into the nature of other varieties of muscle cramps future research will show.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume X: Dermatology and Syphilology.* Associate Editor: C. GUY LANE, M.D., Instructor in Dermatology and Syphilology, Harvard Medical School. lxviii + 1043 pages, 286 illustrations. D. Appleton-Century Company, Inc., New York. 1936. Price, $10.00 a volume.

The tenth volume, Dermatology and Syphilology, of The Practitioner's Library of Medicine and Surgery, is a very well planned addition to this series, the preceding volumes of which have been noticed from time to time in the ANNALS. This book profits by the advantage derived from having a limited number of contributors, for the monographic treatment of a relatively large field promotes balance and thoroughness. Thus we find, among the larger divisions of the volume, General Considerations, by C. Guy Lane, constituting a chapter of 99 pages, covering all of the fundamental considerations of histology, physiology, basic lesions, diagnostic methods and general therapy. The second chapter dealing with Infections of the Skin, by Frederick D. Weidman, requires 200 pages and is admirably done in the concise, illuminating style of which he is a master. Again, the chapter on Syphilis, by J. E. Moore, is 189 pages in length. Thus this volume is in fact a group of treatises upon major divisions of dermatology and syphilology by experts in those particular fields.

As with other volumes of this series the technical book-making is excellent, and the errors over which reviewers are prone to gloat, extremely few. Perfection has, of course, not been attained. For instance, Figure 8 on page 843 appears in the list of figures as a chancre of the lip, although the legend accompanying the figure states that a chancre is precisely what the lesion depicted is *not*. Seldom have large volumes, such as the members of this series, appeared with as few typographical errors as these have shown.

In general, this volume is fully in harmony with the modern trend which relates Dermatology intimately to the practice of Internal Medicine. Skin diseases are no longer to be considered as isolated external phenomena, known by purely descriptive terms; but rather as the superficial manifestations of disease states affecting the entire body economy. The needs of the general practitioner have been kept in mind; the growing importance of occupational diseases of the skin recognized, and a thoroughly practical discussion of syphilis provided. The liberal use of illustrations and the very complete index add to the value of this book as a reference work in the recognition and treatment of the skin conditions which so often come to the attention of the general practitioner.

C. V. W.

Lactobacillus Acidophilus and Its Therapeutic Application. By LEO F. RETTGER, MAURICE N. LEVY, LOUIS WEINSTEIN and JAMES E. WEISS. 203 pages; 14 × 21 cm. Yale University Press, New Haven, Conn. 1935. Price, $2.50.

This volume represents an interesting study of a phase of therapeutics not commonly used by the average physician. The authors establish the bacteriological properties of the acidophilus group of organisms and draw attention to the inaccurate nomenclature employed by certain investigators. This is particularly true concerning the oral and dental types of lactobacilli which have been confused with *B. acidophilus.*

The authors stress the fact that acidophilus milk is not a cure-all. However, it is useful in instances in which the complaint is directly referable to the gastro-

intestinal tract and especially in cases of simple chronic constipation as well as in many other types of constipation. They believe that other laxatives interfere with the effectiveness of the acidophilus treatment and therefore should be omitted. However, the importance of the oral administration of dextrin and lactose in prolonging the activity of an acidophilus implantation is stressed.

A routine plan of administering *B. acidophilus* in the form of milk is outlined. Even under such conditions implantations were obtained only in certain groups of cases and then often only after several courses of treatment. Of the patients who responded favorably a large percentage became so-called "implanters." Satisfactory results were obtained in many cases of "mucous colitis" or "irritable colon" and in a number of cases of diarrhea associated with ulcerative colitis.

Although these investigations seem promising one has the feeling as one reads the book that inasmuch as the acidophilus group of organisms are short-lived and require constant feeding in order to maintain the acidophilus implantation it is doubtful whether one can hope to obtain a continuous therapeutic effect even in those cases in which implantation has apparently taken place for a period of weeks. Moreover, the authors have observed that continual replenishment of the acidophilus strain by ingestion of acidophilus milk is necessary in the great majority of patients.

S. M.

The Extra-Ocular Muscles. By LUTHER C. PETER, M.D. 351 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1936. Price, $4.50.

This second edition of Dr. Peter's book contains 351 pages with 136 engravings and five colored plates. It is divided into six parts as follows: Part I, Anatomy and Physiology; Part II, Heterophoria; Part III, Heterotropia or Concomitant Squint; Part IV, Paralytic Squint; Part V, Surgical Technique; and Part VI, Nystagmus or Talantropia.

In Part I the anatomical illustrations and descriptions are largely from Whitnall's "Anatomy of the Human Orbit" and are most excellent. That portion which deals with the physiology of the muscles is clearly written and illustrated. Parts II and III devoted to the non-paralytic phorias and tropias are sufficiently clear so that not only the specialist but the internist as well will be able to classify these defects. Part IV which deals with the diplopias and paralytic squints is very clear and explicit. By referring to plates 4 and 5 one should theoretically at least be able to diagnose any type of muscle palsy. Unfortunately, however, most cases are so complicated that even the authorities are often unable to determine just what muscle or group of muscles is involved. In Part V the author describes the surgery of the ocular muscles and outlines the technic of those operations which have been most successful in his hands. In many instances the methods are original while in others they are modifications of previously described operations.

The reviewer regrets that the author did not include the surgery of ptosis as well since this is due to abnormalities of the levator palpebrarum which he describes in the anatomical section.

The publishers as well as the author should be commended for this second edition which brings the subject up to date and thereby fills a want not only for the internist but more especially for the ophthalmologist.

C. A. C.

Treatment in General Practice. (Articles republished from the British Medical Journal.) 260 pages; 15 × 22 cm. Paul B. Hoeber, Inc., New York. 1936. Price, $3.50.

The book consists of a number of short articles of variable value on the treatment of certain diseases of the respiratory and cardiovascular systems as well as of certain specific fevers. The editorial policy has been to insist on clarity "to the

point of dogmatism" and there is no doubt but what this objective has been attained. In the section on diseases of the respiratory tract there are many points in symptomatic therapy which physicians in this country will find interesting and valuable, but in general there is little which has not long been included in general practice. A few recommendations are made which are astonishing. "When the patient (with pneumonia) is seen within the first three days a vaccine or a serum should be given. A vaccine has the great advantage that it can be carried in the bag and is immediately available." Under the treatment of asthma by desensitization it is said that "it is better to employ a solution of the four common irritants as one or more of them will be specific for the case, while the others will have a non-specific effect." For technic and dosage the reader is referred to the manufacturer of this solution.

The section on the treatment of certain contagious diseases well repays careful reading though in the article on septicemia the attitude of the writer seems decidedly uncritical.

There is also a great deal of value to certain of the articles on treatment of cardiovascular diseases. In summary, however, the chief interest of the book to the American readers will lie in the opportunity it affords to compare the routine of practice in this country with that in England.

M. C. P.

Prescription Writing and Formulary. The Art of Prescribing. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine, with a foreword by Lewellys F. Barker, M.D. 351 pages; 16 × 23.5 cm. J. P. Lippincott Co., Philadelphia. 1935.

In the writing of this book, Dr. Solomon proposed to bring before the reader the use of drugs in the treatment of disease providing a sound and scientific basis for prescription writing. The book is divided into three parts. Part I is of an introductory nature containing the history of prescription writing from ancient through medieval and modern times. Also there are many practical suggestions to the young physician, such as the prescribing of official remedies rather than proprietary medicines of a more expensive nature. Interesting comments are made on the relationship of the physician and the pharmacist and also on the character and relative usefulness of drugs which are carried in the doctor's handbag. In this section also the absorption and excretion of drugs are discussed in addition to the various avenues of administration. Part II deals with such practical subjects involved in prescription writing as the preparations of solutions, metrology, the use of English and Latin in prescriptions, incompatabilities, construction of the prescription, posology and suggestions for prescription writing. Part III is somewhat separate from the other part of the volume and deals with a number of prescriptions and formulas used in the treatment of the various diseases of the systems of the body. Thus, under drugs having local action, the demulcents and emollients are set forth in typical prescriptions. Under drugs acting on the gastrointestinal tract, the stomachics, antacids and cholagogues are mentioned. In addition there is included a group of biological products illustrating the use of the various serums, vaccines, and antitoxins.

On the whole this volume by Dr. Solomon is well written and excellently organized and will serve a very timely need if it reaches the hands of the young practicing physician. Although essentially a book of practical therapeutics its pharmacological foundations are sound. Dr. Solomon adheres to the modern principle of simplicity in prescribing and in practically all of the formulas and typical prescriptions included in the book a marked departure from the typical polypharmacal prescriptions is noted.

On the whole the author fulfills his purpose in writing this volume and in the reviewer's mind it deserves careful consideration among those physicians who still believe that drugs are an important part of the physician's armamentarium.

J. C. K., JR.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the following gifts received recently for the Library of the American College of Physicians from the authors:

Dr. John Favill (Fellow), Chicago, Ill.—1 book, "The Relationship of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus";

Dr. Samuel Weiss (Fellow), New York, N. Y.—1 book, "Diseases of the Liver, Gall Bladder, Ducts and Pancreas"; 1 bound set, "Clinical Lectures on Gastroenterology," and four reprints;

Dr. C. Frank Brown (Fellow), Dallas, Tex.—2 reprints;

Dr. David N. Kremer (Fellow), Philadelphia, Pa.—2 reprints;

Major James Stevens Simmons (Fellow), M.C., U. S. Army—1 reprint;

Dr. William C. Cooke (Associate), San Diego, Calif.—2 reprints;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint.

Puerto Rico Meeting of Members of the College

The first formal meeting of the members of the American College of Physicians residing in Puerto Rico was held May 26, 1936, with Dr. Ramon Suarez, Governor, presiding.

Dr. Juan Pons, Dr. Harry P. Colmore, Dr. Antonio Ortiz, Dr. O. Costa Mandry, R. R. Rodriguez Molina, Dr. Guillermo S. Marques and Dr. Munoz McCormick were in attendance.

Dr. Suarez, as Governor, was appointed to act as president of the local chapter, and Dr. O. Costa Mandry was appointed secretary. It was decided to hold a meeting with a medical program once every two months. The next meeting will be held at the University Hospital, and will consist of clinical conferences and the presentation of cases.

Dr. W. McKim Marriott (Fellow), for several years Dean and Professor of Pediatrics at Washington University School of Medicine, St. Louis, has been appointed Dean and Professor of Research Medicine at the University of California Medical School, San Francisco.

Major James Stevens Simmons (Fellow) of the Army Medical Research Board, Ancon, C. Z., was elected president of the Medical Association of the Isthmian Canal Zone, at a meeting of this organization on June 16, 1936.

Dr. Ellen C. Potter (Fellow), Director of Medicine, Department of Institutions and Agencies of the State of New Jersey, was the recipient of the honorary degree of Doctor of Laws at the commencement of Rutgers University on June 6.

Dr. Bernard Langdon Wyatt (Fellow), Tucson, Ariz., was unanimously voted the James M. Stacey Award for 1936 by the Faculty Council of the College of Medi-

cine, University of Cincinnati, on June 6. The Stacey Award consists of a medal and an honorarium of $100.00, and is given for significant contribution in the field of focal infection.

Dr. Samuel E. Munson (Fellow), Springfield, Ill., presented a paper on "The Clinical Aspects of Amebiasis" before the annual meeting of the Illinois State Medical Society at Springfield, in connection with a symposium on "Amebiasis," presenting all the phases of the Chicago epidemic of 1933.

Dr. Hugh B. Campbell (Fellow), Norwich, Conn., has been elected vice-president of the Connecticut State Medical Society for the coming year.

Major Raymond O. Dart (Fellow) of the Army Medical Museum, Washington, addressed the Washington Ophthalmological Society recently on "Ocular Tumors."

Friends and students of Dr. Anton J. Carlson (Fellow), professor and chairman of the department of physiology, University of Chicago, presented to the University a bust of Dr. Carlson, the unveiling ceremonies taking place June 1. Dr. Carlson was born in Sweden. He came to America in 1891 and studied at Leland Stanford University in California. After two years of teaching and research at Stanford University and the Carnegie Institution, he became assistant professor of physiology on the staff of the University of Chicago, and in 1914 was advanced to a full professorship.

Life membership in the State Society of Iowa Medical Women was conferred upon Dr. Jeannette Dean Throckmorton (Fellow), recently.

Dr. John A. Foley (Associate), heretofore associate professor of medicine, Boston University School of Medicine, has been named clinical professor of medicine in that institution.

Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y., was awarded the honorary degree of Doctor of Science at the annual commencement of the Medical College of Virginia, Richmond, on June 2.

A testimonial dinner was recently tendered Dr. Charles W. Burr (Fellow), Philadelphia, by his friends on the occasion of the fiftieth anniversary of his graduation in medicine and his election to the presidency of the Medical Alumni Society of the University of Pennsylvania. Dr. Daniel J. McCarthy (Fellow) was toastmaster.

Dr. James H. Means (Fellow and president-elect) will be one of the lecturers on the program of the twentieth annual course of medical lectures and clinics presented by the University of Washington during the week of July 20.

Dr. John G. FitzGerald (Fellow), Toronto, has resigned as dean of the Faculty of Medicine of the University of Toronto, in order to make a survey of methods of teaching preventive medicine sponsored by the Rockefeller Foundation. Dr. FitzGerald, with Dr. Charles Edward Smith of Stanford University School of Medicine assisting, will visit medical schools throughout the United States, Canada, the British Isles and European countries. After the completion of the survey, Dr. FitzGerald will return to Toronto as director of the school of hygiene and of the Connaught Laboratories of the University there.

Dr. Joseph M. Hayman, Jr. (Fellow), Cleveland, has been elected secretary of the American Society for Clinical Investigation.

Dr. Chester M. Jones (Fellow), Boston, and Dr. Ernest H. Gaither (Fellow), Baltimore, have been elected president and vice-president, respectively, of the American Gastro-Enterological Association.

Dr. Henry C. Sweany (Fellow), Chicago, will represent the United States in respect to the discussion of the biologic subject, "Radiological Aspects of the Pulmonary Hilum and Their Interpretation," at the tenth conference of the International Union against Tuberculosis, in Lisbon, Portugal, September 7 to 10.

Dr. Fred H. Kruse (Fellow) and Dr. Harry C. Shepardson (Fellow) have been made clinical professor of medicine and associate clinical professor of medicine, respectively, on the faculty of the University of California Medical School, San Francisco.

Dr. Theodore G. Klumpp (Associate), assistant clinical professor of medicine, Yale University School of Medicine, has been given a leave of absence for the academic year 1936 to 1937 to make a study of glandular and antianemic preparations with the Food and Drug Administration of the U. S. Department of Agriculture, Washington.

Dr. Daniel L. Finucane (Associate) has been appointed associate professor of clinical medicine at Georgetown University School of Medicine, Washington, D. C.

Dr. Coursen B. Conklin (Fellow) has been reëlected secretary of the Medical Society of the District of Columbia.

Under the presidency of Dr. Louis H. Fligman (Fellow), Helena, Mont., the Medical Association of Montana held its fifty-eighth annual meeting at Billings, Mont., July 8 to 9. Dr. Ernest D. Hitchcock (Fellow), Great Falls, and Dr. Allen R. Foss (Fellow), Missoula, delivered papers on "Highlights in Routine Gastric Examinations" and "Manifestations of Allergy in General Practice," respectively.

The Catawba Valley Medical Society met on May 26 at Morganton, N. C., with the following guest speakers from the membership of this College:

Dr. John Russell Twiss (Fellow), New York City, "Differential Diagnosis and Clinical Management of Different Types of Gall-bladder Disease";

Dr. Milton A. Bridges (Fellow), New York City, "Dietary Management of Gall-bladder Disease";

Dr. Isaac H. Manning (Fellow), Chapel Hill, N. C., "Hospital Saving Association of North Carolina."

Dr. Samuel D. Ingham (Fellow), Los Angeles, has been elected vice-president of the American Neurological Association.

Under the presidency of Dr. Julius H. Hess (Fellow), the Chicago Medical Society held its annual banquet and the installation of new officers on June 17.

Dr. Ernest E. Irons (Fellow) is retiring as dean of Rush Medical College to assume the title of professor of medicine. Dr. Irons will remain as chairman of the department of medicine. Announcement has been made that the School of Medicine of the Division of Biological Sciences at the University of Chicago and Rush Medical College are now combined in one institution to be known as the Rush Medical College of the University of Chicago. Undergraduate medical education will be continued at the west side school. The medical schools are united in one departmental organization under the dean of the biological sciences. Dr. Emmet B. Bay will act as associate dean on the west side. It is said that the number of medical students will be greatly diminished during the next five years and graduate instruction will be introduced on an increasing scale, with the possibility that eventually graduate study may supersede undergraduate study entirely on the west side.

Dr. John Richards Aurelius (Fellow), St. Paul, Minn., has been elected president of the Minnesota Radiological Society.

Dr. Thomas Hodge McGavack (Associate), San Francisco, has been appointed associate professor of medicine at the New York Medical College and Flower Hospital, beginning July 1.

Dr. William D. Stroud (Fellow), Philadelphia, has been elected president of the Philadelphia Heart Association.

Dr. Joseph McFarland (Fellow), professor of pathology, University of Pennsylvania School of Medicine, retired June 30, having reached the age limit. He will continue as professor of pathology in the Evans Dental Institute and the Veterinary School, both departments of the University of Pennsylvania.

Dr. Henry K. Mohler (Fellow) has been promoted to associate professor of therapeutics at Jefferson Medical College, Philadelphia.

Dr. Guy W. Wells (Fellow), Providence, R. I., was elected secretary of the Rhode Island Medical Society at its annual meeting, June 3.

Dr. Hugh S. Cumming (Fellow), Washington, D. C., is chairman of the Washington committee on arrangements for the Second National Conference on College Hygiene to be held in Washington, D. C., December 28 to 31, under the joint sponsorship of the American Student Health Association, the National Health Council and the President's Committee of Fifty on College Hygiene. It is announced that there will be no formal program with prepared addresses, but the work will be divided into five sections: health service, health teaching, organization and correlation, special problems and relationship of college hygiene to teacher training and secondary education. Dr. Livingston Farrand, president of Cornell University, is chairman of the conference.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, Dr. David J. Davis (Fellow), Chicago, Dr. Paul J. Hanzlik (Fellow), San Francisco, Dr. Russell L. Cecil (Fellow), New York City, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, are members of the College who appeared on the formal program of the fifteenth annual meeting of the Pacific Northwest Medical Association in Portland, Ore., July 8 to 11.

Dr. Virgil E. Simpson (Fellow), Louisville, Ky., was guest speaker on May 19, 1936, at the meeting of the Southwestern Medical Society at Paducah, Ky. His subject was "The Physician, The Pharmacopoeia, Prescriptions and Philandering." Dr. Simpson was also the guest speaker at the Harlan County Medical Society at Harlan, Ky., on May 30, 1936. Subject: "The Social Security Act and the Medical Profession."

Dr. Charles James Bloom (Fellow), Professor of Pediatrics, Post-Graduate School of Medicine, Tulane University of Louisiana, was one of the guest speakers of the State Medical Association of Texas before the Section on Medicine and Diseases of Children and the General Meeting, held in Houston, Texas, May 26, 27, 28, 1936.

Dr. Herbert T. Kelly (Fellow), Philadelphia, was guest speaker June 9, at the meeting of the Cumberland County (New Jersey) Medical Society. The subject of his address was "Diabetes."

OBITUARIES

DR. ALDEN H. WILLIAMS

Dr. Alden H. Williams (Fellow), Grand Rapids, Mich., died June 10, 1936, of coronary occlusion; aged, 59 years.

Dr. Williams was born at South Gibson (Susquehanna County), Pennsylvania, and attended the Bloomsburg State Normal School. He, however, became interested in medicine and entered the University of Michigan in 1894, receiving his medical degree in 1899. He did postgraduate work in Berlin, Germany, during 1907, and pursued several postgraduate courses, especially in radium and roentgen-ray therapy, in this country in later years. During the World War he was in the Radiological Service of the U. S. Veterans Bureau. He later became Chief of Staff of the Butterworth Hospital in Grand Rapids. He was a past president of his county medical society, a member of the Michigan State Medical Association and a Fellow of the American Medical Association. His interests were primarily in the field of radiology, and hence he was an active member and former president of the Radiological Society of North America, a member of the American Roentgen-Ray Society and other organizations in this field. He became a Fellow of the American College of Physicians in 1922.

DR. ALANO E. PIERCE

Dr. Alano E. Pierce (Fellow), Minot, N. D., died March 14, 1936, of pneumonia; aged, 35 years.

Dr. Pierce was born at Dexter, Minnesota, April 22, 1900; he received the degree of Bachelor of Arts from the University of Minnesota in 1921, the degree of Bachelor of Science from the same institution, 1923, the degree of Bachelor of Medicine from the University of Minnesota Medical School in 1924, and his degree of Doctor of Medicine from the same institution in 1925. He did post-graduate study at the University of Vienna from February to November, 1926. He became Assistant in Medicine at the University of Minnesota Medical School in January, 1927. His internship was spent at the Minneapolis General Hospital. He went to Minot, N. D., in 1929, and became a member of the regular staff of the Trinity Hospital and became associated with the Northwest Clinic as Internist.

He was a member of the Northwest District Medical Society, the North Dakota Medical Society and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians on March 22, 1931.